vol 16 no 4 APRIL 59

Journal of Pharmacy

official publication of the American Society of Hospital Pharmacists

HOW TO PREPARE A PHARMACY BULLETIN

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Dear Sirs:

American Hospital Formulary Service

DEAR SIRS: We have received our copies of the American Hospital Formulary Service and find it to be everything it was said to be. . .

WILFRED L. HUFTON, *Administrative Assistant*
New York University-Bellevue Medical Center
of New York University
New York, New York

DEAR SIRS: Congratulations on the Formulary. A hurried inspection reveals it as a masterpiece of patient planning and research—truly worth waiting for.

SISTER M. FLORENTINE, *Chief Pharmacist*
Mount Carmel Hospital
Columbus, Ohio

DEAR SIRS: We have recently received our initial order of five copies of the American Hospital Formulary Service. We find this an excellent collection of monographs and other essential information. The Committee on Pharmacy and Pharmaceuticals deserves much thanks for their time and efforts in making this publication possible. . . . we would like to order additional copies to be placed in various strategic areas in our institution.

CEDRIC M. JEFFERS, *Chief*
Pharmacy Service
Scott and White Memorial Hospitals
Temple, Texas

DEAR SIRS: I have just received a copy of the American Hospital Formulary Service and find it excellent with the exception of a mechanical problem due to an error in punching the holes in the pages. Also, it would be advantageous to print at least the title page on heavier paper.

DUANE D. DEAKINS, M.D.
Medical Director
San Joaquin General Hospital
Stockton, California

DEAR SIRS: We have received our copies of the new American Hospital Formulary Service and everyone (Physicians, Nurses, et al) is immensely impressed and pleased. More power to the Formulary Service Committee that put Pharmacy ahead in this endeavor.

GEORGE J. GRUBER, *Pharmacist*
U. S. Public Health Service Hospital
Savannah, Georgia

Education and Hospital Pharmacy

DEAR SIRS: The following is a copy of a letter sent to Mr. Robert C. Bogash stating our position regarding the six year program and a Doctor of Pharmacy degree.

"The Hospital Pharmacists' Association of Greater St. Louis wishes to officially endorse a six year academic program leading to the degree of Doctor of Pharmacy. It is our recommendation that the AMERICAN SOCIETY OF HOSPITAL PHARMACIST should do all in its power to encourage adoption of a six year program and the Doctor of Pharmacy degree.

"The requirements of modern day hospital pharmacy necessitate increasing the professional training and stature of its members. This may best be accomplished by vigorously encouraging colleges of pharmacy to provide prospective hospital pharmacists with the requirements of their chosen profession. A campaign sponsored by the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS to promote member activity toward adoption of the six year program and the Doctor of Pharmacy degree would do much toward attainment of this necessary goal.

"The future growth of the profession of hospital pharmacy is dependent upon our willingness to assume the duties and responsibilities of a Doctor of Pharmacy."

I am sure you will find it of interest, for in essence it endorses what you have so eloquently expressed in your editorial "An American School of Hospital Pharmacy."

JOHN C. GRIFFIN, *Secretary*
Hospital Pharmacists' Association of Greater St. Louis
St. Louis, Missouri

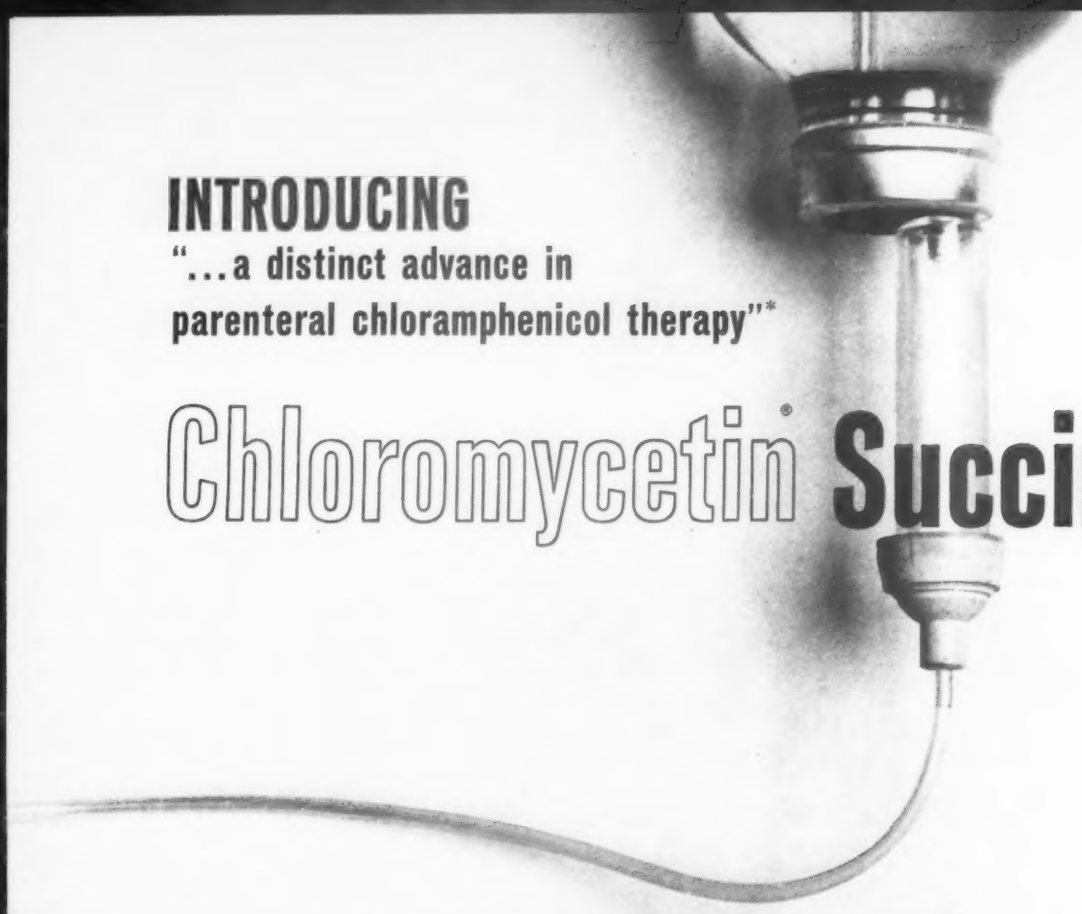
DEAR SIRS: Your editorial on "An American School of Hospital Pharmacy" was fine and thought provoking. It is one of those areas in which something "should" have been done a long time ago.

JENNIE M. BANNING, *Chief Pharmacist*
Saginaw General Hospital
Saginaw, Michigan

INTRODUCING

"...a distinct advance in parenteral chloramphenicol therapy"*

Chloromycetin® Succinate



you can give it intravenously

intramuscularly

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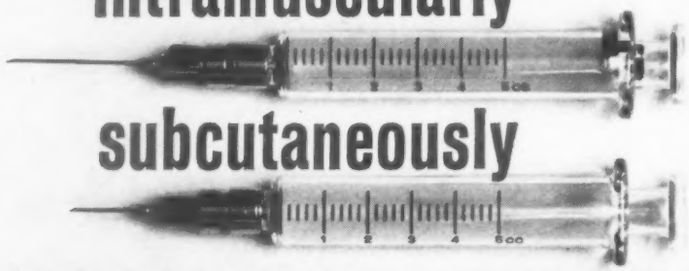

Highly soluble in water or other aqueous parenteral fluids, CHLOROMYCETIN SUCCINATE solution is easily prepared for use by recommended parenteral routes in a wide range of concentrations. Tissue reaction at the site of injection is minimal, permitting continuous daily dosage, even in children.

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CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately, or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

*Ross, S.; Puig, J. R., & Zaremba, E. A., in Welch, H., & Martí-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 817.

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editorial

by DON E. FRANCKE

Outpatient Prescriptions and Hospital Pharmacies

► PHARMACISTS IN RETAIL PRACTICE are often sharply critical of hospitals and hospital pharmacists for filling prescriptions written by members of the medical staff for outpatients. Arguments put forth by retail practitioners run somewhat as follows: A hospital is (1) a tax-free, non-profit institution or (2) an institution run by the local, county, state or Federal government, neither of which should compete with private enterprise by dispensing medication to outpatients.

Let us consider the matter from the viewpoint of the voluntary hospital. First, it should be emphasized that tax-free, non-profit, voluntary hospitals are, in themselves, private enterprises in the sense that they are not managed by or controlled by a governmental unit. They are not private enterprises only in the sense that they do not exist for the purpose of making a profit. It is true that they are supported, in part, by funds raised by the community. But it is also true that they return to the community more than equivalent service through the care of patients unable to pay the complete costs of hospitalization. In fact, voluntary hospitals perform a distinct service to American society by helping those who are self-supporting in health but unable to bear the additional financial burden of sickness. In addition, they care for all those who can pay, in part or in whole, for their medical care. The problem of the voluntary hospital is principally one of income. Free service cannot be provided unless part of the cost of this service is furnished by pay patients as well as by community funds. The pharmacy is one of the few services of the hospital which can be called upon to make up deficits.

While retail pharmacists protest the filling of outpatient prescriptions by hospital pharmacists, the basic consideration from society's point of view is not what pharmacists do the dispensing but that the dispensing be done by pharmacists. True, such practices do affect the profession of pharmacy but not to the extent or for the reasons our colleagues would have us believe.

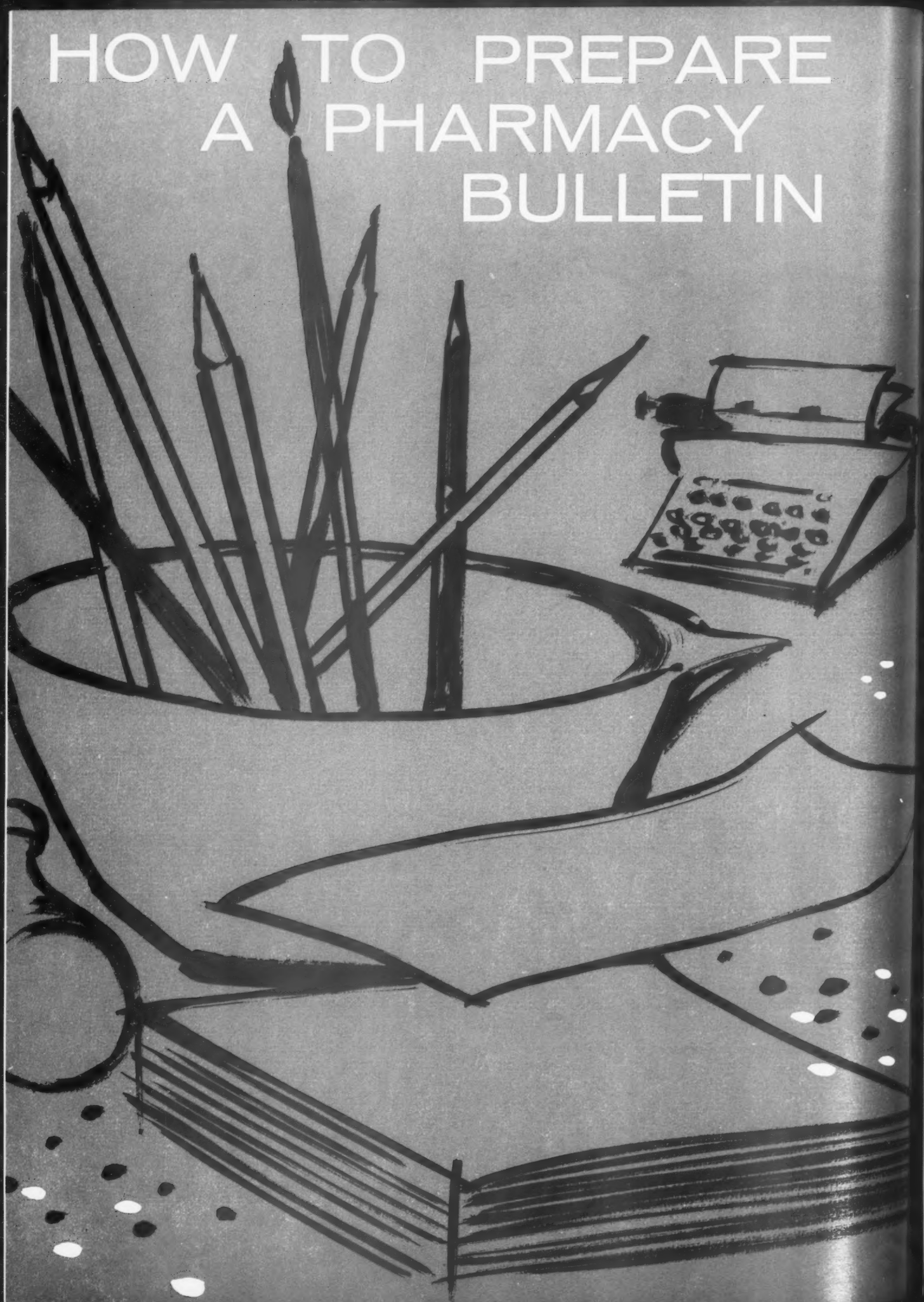
There are at least two other considerations that merit mention. Consider a tax-free, non-profit hospital employing a chief pharmacist and three staff pharmacists and a retail pharmacy with the owner-proprietor and three employee pharmacists. In the case of the retail pharmacists, the employees are paid a salary. The owner-proprietor pays several taxes on his business but the profits of the enterprise are his. In the case of the hospital pharmacists, all are paid a salary and the excess over expenses from the operation of the pharmacy goes to the hospital to provide additional services to the community or to make up deficits of non-revenue producing departments. In either case, the money is used by the community, directly or indirectly, for further services. All of the pharmacists pay a tax upon their income. Thus, while it is true that the hospital does not pay a tax, as such, it gives to the community the equivalent of taxes in the form of services to the indigent and the medically indigent.

Second, consider the example cited from the point of view of pharmacy as profession. In each case, retail and hospital, we have three pharmacists working under the direction of a fourth. Is not the economic welfare of these also important? In general, retail pharmacists enjoy significantly higher incomes than do those in hospital practice. Hospital salaries are lower, in part, because hospital rates have never caught up with the cost of providing the expanding health services now offered and also because hospital salaries for generations have been substandard. Granted that hospital practice offers numerous professional challenges and opportunities for service, why should hospital pharmacists be penalized economically by choosing hospital pharmacy as a career? Should not efforts be made to make hospital pharmacy as attractive economically as it is professionally? Can this be done by curtailing the income of the hospital by not filling prescriptions for outpatients? Can we say that it is important for a pharmacist outside of the hospital to have a good income but unimportant to the hospital pharmacist? Is it reasonable to expect hospitals to supply free medication to the indigent without recovering some of their costs by charging those able to pay?

The question of filling outpatient prescriptions will ultimately be decided upon the basis of what is best for society as a whole. At present, large groups of society are seriously concerned with the preservation of the voluntary hospital system. The situation is serious and the pressures are great to have the government play a more active role in medical care. However, many are convinced that humanitarian idealism still plays a significant role in medical care and that society will be best served by preserving the voluntary hospital system. Faith, hope, and charity are even more important to the sick and these are not easily dispensed as a "service" by remote control.

The question of outpatient prescriptions is a complex one and we do not claim to have all the answers. It merits extensive debate by hospital and retail practitioners.

HOW TO PREPARE A PHARMACY BULLETIN



by WILLIAM E. HASSAN, JR., *and* ERNEST S. LENTINI

► IT IS A WELL ESTABLISHED FACT THAT the methods of disseminating interdepartmental information in many hospitals have not been sufficiently developed whereby they adequately serve the institution's needs.

One area, the pharmacy, is in the enviable state of being handicapped in its operation by this apparent lack of communication and yet is in an excellent position to make a valuable contribution towards solving the problem.

The obvious solution, from the point of view of the pharmacy, is to develop a Pharmacy Bulletin or Newsletter. This department is chosen for the task because its method of operation brings it into close contact with the major hospital services as well as the members of the medical staff.

The preparation of a worthwhile pharmacy publication requires a great deal of time and forethought. It is our intent to, in this paper, provide some ideas relative to possible contents, format, duplication, and distribution of such an educational and informative medium.

Selection of A Title

The title selected for the publication should be specific, short and of such a nature that it identifies the publication as well as its contents.

WILLIAM E. HASSAN, JR., Ph.D. is Assistant Director, Peter Bent Brigham Hospital and Professorial Lecturer, Massachusetts College of Pharmacy, and ERNEST S. LENTINI, B.Sc., is Pharmacist-in-Chief, Peter Bent Brigham Hospital, Boston, Massachusetts.

Too often, a title is selected which imparts the impression that the publication is a collegiate gossip paper rather than a professional journal.

Examples of good titles are: Pharmacy Bulletin, Pharmacy News, Pharmacy Review, and Pharmacy Newsletter.

Examples of titles which, in the opinion of the authors, are not acceptable are: The Mortar and Pestle, The Pill Roller News, Drug Store News, News Capsule, etc.

Contents

Since the purpose of this publication is to educate as well as to inform, it is imperative that its contents be of such a nature to attain this goal.

In general, the publication should be divided into five categories. They are as follows:

A. Editorial.

B. New Drug Section.

C. Abstract of the Pharmacy Committee Meeting.

D. Lead articles by prominent members of the medical staff.

E. General.

The editorial, prepared by the Pharmacist-in Chief, should be a means whereby new procedures relative to ordering, prescribing, storage or administration of drugs within the hospital are introduced and publicized. It may also be used to focus attention on infractions of established procedures and to editorialize therapeutic trends and opinions.

JEFFERSON HOSPITAL PHARMACY NEWS

Vol. V January, 1958 No. 1

HAPPY NEW YEAR

Pharmacy Service extends best wishes to the Medical Staff for a happy (without tranquilizers) and successful New Year.

As one of our New Year resolutions we are re-naming publication of the "Pharmacy News", with the best intentions of greeting you this way monthly throughout the year.

AUTOMATIC STOP ORDER FOR NARCOTICS ORDER

On recommendation of The Pharmacy Committee, the Attending Staff approved that "All drug orders for narcotics [administered orally or parenterally] shall be automatically discontinued after 48 hours, unless:

1. The order indicated an exact number of doses to be administered.
2. An exact period of time for the medication is specified, or
3. The attending physician reorders the medication.

All reorders must be written on the treatment sheet by a physician. It is recommended that short acting preparations, i.e. time limit be set for orders for sedatives and hypnotics, antiemetics and antidotics."

PRESCRIBING OF NARCOTICS BY UNLICENSED INTERNS AND RESIDENT PHYSICIANS

On recommendation of The Pharmacy Committee, the Attending Staff approved that "A chief may discontinue an order for a narcotic but he must endorse this order within twenty-four hours. The intern will be held responsible for directing the attention of a resident physician [who possesses a Pennsylvania narcotic license] or hospital staff physician to the requirement for signature. Attending physicians must sign with name and license number each narcotic order on treatment sheets of the hospital. No time unlimited "P.R.N." orders are allowed".

PRESCRIBING OF DOSAGE RANGE BY PHYSICIAN

On recommendation of The Pharmacy Committee, the Attending Staff approved that physicians on the hospital staff be discouraged from prescribing a dosage range for any medication and in addition, it recommends that where a two dosage schedule is ordered, i.e. "Heparin by injection, gtts/10 to 1/12 min.", the nurse be instructed to administer only the lower dose.

LABELING OF DRUGS

On recommendation of The Pharmacy Committee, the Attending Staff approved that the physicians on the staff be discouraged from prescribing "Injection of choice," and that they should discover the injection of choice for the particular patient and prescribe same, and not leave that responsibility to the nurse or other non-physician personnel.

THE METRIC SYSTEM

On recommendation of The Pharmacy Committee, the Attending Staff approved that the metric system be made mandatory for use by the intern and resident staff in all of their prescribing.

MEDICATION BROUGHT BY THE PATIENT TO THE HOSPITAL

On recommendation of The Pharmacy Committee, the Attending Staff approved the fact that no medication brought to the patient's bedside. Pharmacy staff be reassured that the physician is presented to be at the patient's bedside. Further, if such drugs from home are essential, and the patient does not desire to pay for additional supply of the drug from the Hospital Pharmacy, that the physician should label the drug container brought from home and instruct the patient how, and that the physician should order on the treatment sheet the medication as labeled.

DEFINITION OF DRUGS FOR THE HOSPITAL FORMULARY

On recommendation of The Pharmacy Committee, the Attending Staff approved that the following definitions and categories be used in an effort to clarify certain aspects of drug approval for the Hospital Formulary:

1. Drugs Recommended for the Formulary - is a therapeutic agent recommended as essential for the best patient care, use whose place in therapy is well established and promotional. These drugs are listed in the Hospital Formulary.

2. Drugs Approved for Evaluation or Clinical Trial is a pharmacologically available drug which has not been approved by the Pharmacy Committee for inclusion to the Formulary. Such a drug should be reviewed every three months for a time period and then either (1) fully approved, or (2) discontinued. Such a drug shall be placed in stock in the Hospital Pharmacy or the Clinic (Out-patient) Pharmacy during its trial period, for issue through the Pharmacy to both in-patient and out-patients.

3. Investigational Drug - a drug which has not yet been released by the Federal Food and Drug Administration for general use and is not available commercially. An Investigational Drug is used under the close supervision of the chief investigator who personally controls the use and distribution of said drugs. The chief investigator shall register with the Secretary of the Pharmacy Committee, the name, address or other identity of such investigational drug together with the name or names of those physician personnel possessing a stock of said drug.

NEW ASSISTANT DIRECTOR OF PHARMACY SERVICE

We regret the loss of Joseph A. Dzeikevic, the Assistant Director of Pharmacy. Joe is now Director of Pharmacy Service at Delaware County Hospital. Mr. Neil W. Davis, who received his M.Sc. in Pharmacy at the Phila. College of Pharmacy & Science, and who served a Residency in Pharmacy at Jefferson, has been appointed to this position.

Editorial Staff - - Frank Fox and Norbert Plass

The new drug section should contain the major data on each new drug accepted for use within the hospital by the Pharmacy Committee. Major information in this instance includes a brief description of the drug, its range of usefulness, indications, side effects, administration and dosage and how supplied by the pharmacy.

The abstract of the minutes of the Pharmacy Committee meeting is a worthy inclusion in the publication in that it keeps the entire staff aware of the constantly changing trend of therapeutics within the institution. In addition, it allows those members of the staff who have had reason to communicate with the Pharmacy Committee to note that their recommendations have received attention.

Each issue should have a lead article by a prominent member of the staff. The article should not be over two pages in length and should be restricted to an evaluation of current pharmaceuticals or trends of therapy within the author's field of specialization.

The section categorized as "General" may include anything which the Editor feels is of interest to the medical staff, nursing service, or laboratory staff. Samples of the type of information which might well be placed in this category are abstracts of releases from the state department of public health, abstracts of articles of interest on current situations such as the recurrence of an outbreak of Asian Flu and abstracts from the various journals relative to unusual sources of poisoning in humans, etc.

Format and Duplication

The format of the publication will vary with the originality of the pharmacist, therefore the following description is provided as a basis for further development by the individual concerned.

The paper selected should be a good quality mimeograph paper measuring 8½″ x 11″. In view of the fact that the first page should be inviting to the potential reader we recommend that the heading be pre-printed. By so doing, you will have the advantage of being able to use stock cuts of pharmaceutical symbols that the printer can obtain for you in order to help you decorate the publication. In addition, you will be able to have each issue have a different colored ink used to print the heading on the white mimeograph paper or on a colored paper stock. Either of the above suggestions wouldn't cost much, but would serve to draw the attention of the potential reader.

In cutting the stencil, it is suggested that the page be longitudinally split in half and the data typed in columns. The advantage of this is that many of the readers like to clip out the data on a new drug and affix it to their Formulary or, in the case of the nursing service, to 3″ x 5″ cards in their new drug file.

The method of duplication will vary with the availability of the necessary equipment within the institution. Either mimeograph, multigraph or multilith will reproduce a neat and attractive publication whose individual pages should be collated and stapled together.

Distribution

The completed issue should be distributed to the following areas and individuals, provided that they exist in the particular hospital:

A. Every member of the medical staff and to the staff library
B. Administration
C. Nursing Service
   1. A copy to each station
   2. Several copies to Nursing School Office
   3. Nursing School Faculty
   4. Nurses' Library
D. Laboratories

Advantages

The preparation of a pharmacy publication requires the time, effort and imagination of the pharmacist who undertakes such a project. On the other hand a well prepared issue can save the pharmacy a great deal of time by reducing the number of telephone calls concerning new drugs or newly instituted procedures.

In addition, it will add to the professional stature of the pharmacist within the institution as well as to give him the satisfaction of having made a contribution towards better communication between his department and the professional staff.

THE PHARMACY NEWSLETTER

a method of establishing good communications

by PAUL G. BJERKE

► IF THERE WERE ONE MORE SINGLE THING THAT you could do in your department to be more helpful to the staff, the hospital, and yourself, it would be the publishing of a Pharmacy Newsletter. I sincerely believe that if you are starting a new department or want to improve an established one, a newsletter or bulletin will be of tremendous help.

I will distribute sample copies of several newsletters which we will discuss, but first, let us consider newsletters in general.

Objectives of Newsletters

Why publish a newsletter? I think there are several important reasons. From it the Pharmacy Department will have an excellent medium, providing information for the staff. It is a medium for becoming closer to the medical staff and also for gaining much prestige for the service the Pharmacy Department is rendering.

In establishing yourself as a consultant, the newsletter can be of tremendous help. A medical staff bulletin can be a very interesting project for the department. Perhaps the main function of the vehicle is to keep the medical staff and the hospital informed of new products, policies, or procedures.

It will, however, add much prestige to your department. It will, no doubt, bring many of the medical staff into your department for further discussion. This is one of the things you should be working toward; the newsletter is certainly one way to accomplish it.

PAUL G. BJERKE is Chief Pharmacist, Luther Hospital, Eau Claire, Wisconsin

Presented at the Institute on Hospital Pharmacy, University of Chicago, Chicago Illinois, July 30, 1958.

Format

The format of the bulletin can be simple or elaborate, depending upon the situation, your likes, and the money one wants to spend on it. If one does not want to use a mimeographed heading, it can be printed at the top of each sheet by a commercial company at a very small cost. Then the bulletin can be mimeographed by the hospital. The printing of the heading may tend to improve the appearance of the bulletin. The heading should contain the name of your hospital, the address, the date, and the volume or number. Although it is not necessary for local use, I like the address of the hospital included because there are times and persons who live in other communities to whom you may wish to send an occasional copy, and then, obviously, it is good to have the address.

In our particular bulletin we have designed the heading so that any department can use it. I will elaborate on this later.

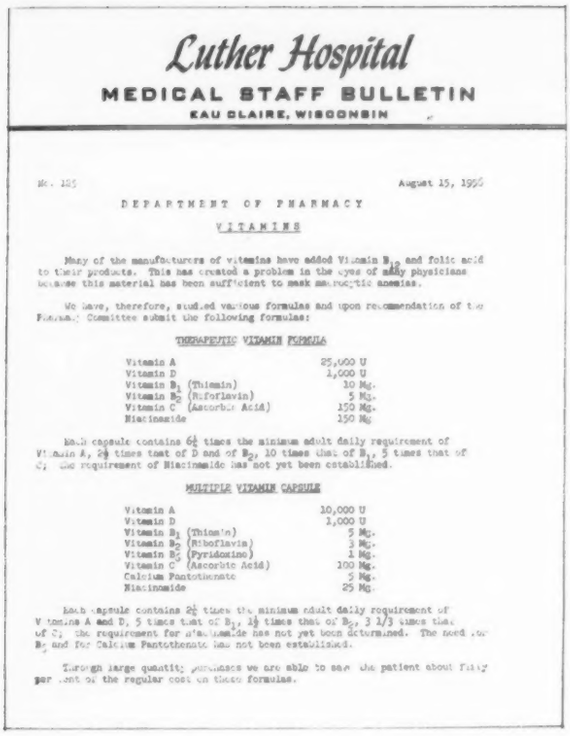
In designing a bulletin it is important to keep the size uniform and to keep in mind some type of file in which it may be kept by the individual. I believe it would be wise to supply the physician with some type of inexpensive binder. If it is to be a loose leaf type, the pages can be punched before distribution.

Material to Publish

The material selected for your newsletter may be the key to success. You may wish to use the bulletin to inform the medical staff on one or more new drugs. You may want to advise them on new antibiotics. You may want to show a cost comparison between various brands of certain products. You may want to give the various brand names for a particular product. I have found that, oftentimes, so much confusion with brand names exists that physicians greatly appreciate such a summary as well as cost comparisons.

In a particular bulletin you may want to report to the medical staff, in writing, some particular action that the Pharmacy Committee has taken. In the instances where formularies are used, additions made to the formulary are listed in the bulletin..

You may want to inform the medical staff of a new procedure that has been started by your department.



Luther Hospital

MEDICAL STAFF BULLETIN

EAU CLAIRE, WISCONSIN

No. 185 August 15, 1948

DEPARTMENT OF PHARMACY

VITAMINS

Many of the manufacturers of vitamins have added Vitamin B_{12} and folic acid to their products. This has created a problem in the eyes of many physicians because this material has been sufficient to mask macrocytic anemias.

We have, therefore, studied various formulas and upon recommendation of the Formulary Committee submit the following formulas:

THERAPEUTIC VITAMIN FORMULA

Vitamin A	25,000 U
Vitamin D	1,000 U
Vitamin B_1 (Thiamin)	10 Mg.
Vitamin B_2 (Riboflavin)	5 Mg.
Vitamin C (Ascorbic Acid)	150 Mg.
Niacinamide	150 Mg.

Each capsule contains 6½ times the minimum adult daily requirement of Vitamin A, 2½ times that of D and of B_2, 10 times that of B_1, 5 times that of C; the requirement of Niacinamide has not yet been established.

MULTIPLE VITAMIN CAPSULE

Vitamin A	10,000 U
Vitamin D	1,000 U
Vitamin B_1 (Thiamin)	5 Mg.
Vitamin B_2 (Riboflavin)	3 Mg.
Vitamin B_6 (Pyridoxine)	1 Mg.
Vitamin C (Ascorbic Acid)	100 Mg.
Calcium Pantothenate	5 Mg.
Niacinamide	25 Mg.

Each capsule contains 2½ times the minimum adult daily requirement of Vitamins A and D, 5 times that of B_1, 1½ times that of B_2, 3 1/3 times that of C; the requirement for niacinamide has not yet been determined. The need for B_6 and for Calcium Pantothenate has not been established.

Through large quantity purchases we are able to save the patient about fifty per cent of the regular cost on these formulas.

For example: For a time we filled orders for Dicumarol, with the daily dose ordered by the physician. We now have standardized on one size tablet and each patient requiring this drug gets a supply. Things that improve the service and simplify the ordering for physicians and nurses are greatly appreciated by them; however, there must be a mode of communication.

Perhaps the pharmacist would like to tell the medical staff how the ordering of certain drugs affects the payments made by insurance companies. Perhaps the department has changed its methods of packaging prescriptions. Many times there is something in the AMERICAN JOURNAL OF HOSPITAL PHARMACY, the *American Professional Pharmacist,* or the *Journal of the American Pharmaceutical Association* that would be of interest to the staff.

I am sure that you will find that your problem, if you can call it such, will be in selecting the material you want to present. I am sure you will have no trouble in finding a wealth of material in which your staff will be interested.

Length and Frequency

The length of the newsletter is something to consider. If you choose to limit yourself to one page it may sometimes be necessary to condense material. Perhaps you will prefer to make your letter two or more pages in length. This could be very easy, especially if one lists additions to a formulary. It perhaps is wise if the releases follow some type of pattern of approximate length.

Both the length and frequency of the bulletin should be given some thought before starting the letter. One school of thought feels that regular, constant releases are the best. That is, every two weeks or every month. These proponents feel the physician will be looking forward to them at the same time and, thus, they will be more effective and better read. The latter is a most important consideration since, obviously, if they are not read by the staff they have really lost their value. On the other hand, some people prefer to release their bulletins as news arises, not sending them at regular intervals. Their feeling is that they will then be sending only the most important news and the physician will recognize it as a most important directive, insuring its being read. Both lines of thought have their merit, and I am sure you are the best person to judge the frequency of release you might maintain.

Cost

The cost of the newsletter will depend on a number of factors. The first consideration will be the elaborateness of your release. A single mimeographed sheet, done in your own hospital, will be the least expensive. Costing slightly more will be the single mimeographed sheet with a printed heading. If the bulletin runs into several pages, again you will find greater cost. The more expensive bulletins have several pages and some have covers. In most cities a mimeographing service is available. If it is not possible for the hospital to do the work this is a fairly inexpensive method.

The best method of distribution is direct mail to each physician. It need not be sent first class but can be sent under the hospital's mailing permit. Other methods of distribution may have other advantages such as at the medical staff meetings or in the doctors' lounge. These latter methods have the possible disadvantage of incomplete distribution. The other disadvantage is that the bulletins, perhaps, will be read but the chances are good that they will not be filed.

It may be desirable in your hospital to combine the release with several other departments. That is, have news from other departments in your bulletin. In the event that nursing distributes a release, perhaps something could regularly be included from the Pharmacy Department. Needless to say, a single release from you would be most effective.

It may be helpful to tell you about the development of our bulletin before comment on the sample copies that I will distribute.

Luther Hospital Bulletin

The *American Professional Pharmacist,* September, 1948, credits the *Luther Hospital Medical Staff Bulletin* as the oldest or at least the longest continuous

periodic publication by a hospital pharmacist or pharmacy for the medical staff of a hospital. Many simple and elaborate bulletins by hospital pharmacists have appeared during the last ten years. This is very commendable, and it is our earnest hope that this trend will continue.

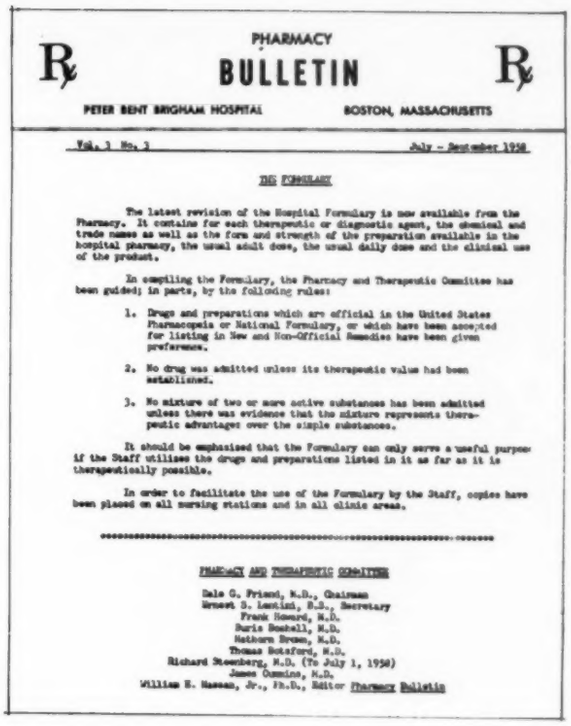
Our objective in issuing a pharmacy bulletin is to present to the entire medical staff information concerning new drugs. Before issuing our bulletin certain basic ideas on its presentation were discussed. We decided that the bulletins would be informative but brief. They would, for the most part, deal with one particular problem or one or two new products. The physician would then be able to tell at a glance if he were interested and would spend very little time in reading the bulletin. If it were a problem with which he was especially concerned and the release did not give him sufficient information, he would naturally come to the Pharmacy for more detailed information. With this inducement in mind, we encourage the return of the physician by never being too busy to investigate any problem, no matter how much time it consumes. We decided that the bulletins would not be issued at any particular time but only when there was something of special interest. Our objective was to make each bulletin valuable to the physician instead of flooding him with inconsequential releases.

Our first pharmacy bulletin was issued in the form of a letter on May 27, 1942. It informed the medical staff of a Vitamin B Complex Elixir that we were manufacturing. The reception of this product was very encouraging, and it is interesting to note that today we use very little, if any other, Vitamin B Complex Elixir.

The encouragement received on the first release, however, was short-lived. Our next release concerned the intravenous use of amino acids, and much to our surprise, it proved to be a failure. In analyzing the situation, we quickly learned that we couldn't interest the entire staff in any certain phase of therapy and that most physicians would prescribe a Vitamin B Complex Elixir, whereas even today few of our staff members are enthused over the use of amino acids intravencusly. We then made it a policy to publish bulletins on subjects which would be of interest to the majority of the staff.

The management was enthused over the medical staff bulletins, and the October 4, 1943 issue was distributed on hospital stationery. Penicillin was then being controlled by the National Research Council, and the subject of this bulletin was the procedure for obtaining it. This proved to be of great interest to the medical staff. In a short time we were making requests for the drug. This, perhaps, was one of our most successful bulletins.

The type of bulletin was changed on November 11,



PHARMACY

℞ BULLETIN ℞

PETER BENT BRIGHAM HOSPITAL BOSTON, MASSACHUSETTS

Vol. 1 No. 1 July - September 1958

THE FORMULARY

The latest revision of the Hospital Formulary is now available from the Pharmacy. It contains for each therapeutic or diagnostic agent, the chemical and trade names as well as the form and strength of the preparation available in the hospital pharmacy, the usual adult dose, the usual daily dose and the clinical use of the product.

In compiling the Formulary, the Pharmacy and Therapeutic Committee has been guided; in parts, by the following rules:

1. Drugs and preparations which are official in the United States Pharmacopeia or National Formulary, or which have been accepted for listing in New and Non-Official Remedies have been given preference.
2. No drug was admitted unless its therapeutic value had been established.
3. No mixture of two or more active substances has been admitted unless there was evidence that the mixture represents therapeutic advantages over the simple substances.

It should be emphasized that the Formulary can only serve a useful purpose if the Staff utilizes the drugs and preparations listed in it as far as it is therapeutically possible.

In order to facilitate the use of the Formulary by the Staff, copies have been placed on all nursing stations and in all clinic areas.

PHARMACY AND THERAPEUTIC COMMITTEE

Dale G. Friend, M.D., Chairman
Ernest D. Lantini, B.S., Secretary
Frank Howard, M.D.
Boris Bostell, M.D.
Matthew Brown, M.D.
Thomas Botsford, M.D.
Richard Steenberg, M.D. (To July 1, 1958)
James Cummins, M.D.
William H. Hassan, Jr., Ph.D., Editor Pharmacy Bulletin

THE BULLETIN

of THE PHARMACY AND THERAPEUTICS COMMITTEE

UNIVERSITY HOSPITAL ANN ARBOR MICHIGAN

Vol. 1 JANUARY - FEBRUARY 1960 No. 1

INTRODUCTION

There exists today a greater abundance of chemical substances of potential medicinal value than at any other time in the history of medicine. This gestures of new drugs submitted for trial in the medical profession has made it difficult to keep abreast of therapeutic advances in the chemical field. THE BULLETIN, of which this is the first issue, marks the inauguration of a new service to the staff members of University Hospital. THE BULLETIN is designed and presented as an aid in keeping the professional staff informed regarding both the availability and use of new drugs and, the replacement and withdrawal of old drugs. It is also intended that THE BULLETIN shall add to and supplement information available in the HOSPITAL FORMULARY.

Present plans call for bimonthly publication as a four page pamphlet, suitable for filing and future reference, in any standard ring type cover. Your committee hopes you will find THE BULLETIN helpful. Suggestions for its improvement are welcomed.

The Committee on Pharmacy and Therapeutics

IN THIS ISSUE

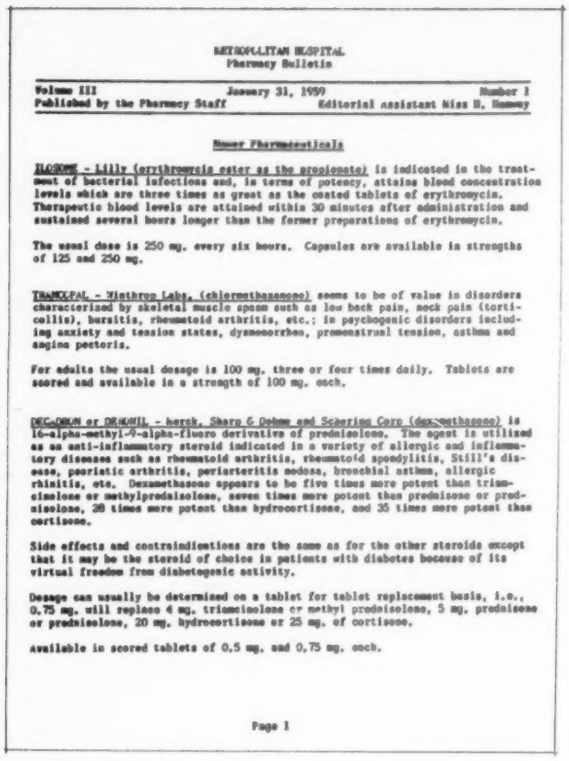
COMMITTEE POLICIES

APPROVAL OF DRUGS ACCEPTED FOR USE IN HOSPITAL

The Committee has adopted the following policy for the approval of drugs accepted for use in the hospital. It has also established procedure for the request of new drugs and dosage forms, as embodied in rule six. All departments are urged to note the following points before requesting approval for new drugs.

1. No drug sold under a proprietary name will be admitted under such a name if a substance of identical composition can be obtained under a non-proprietary name. Prescriptions calling for trade name drugs will be filled with the basic drug, but not necessarily with the brand called for under the registered trade name.
2. No drugs of secret composition will be approved.
3. No drug will be studied, except for controlled research, before its therapeutic value has been established.
4. Department heads shall be notified whenever a previously accepted drug is under reconsideration for deletion, so that they may submit evidence for its retention.
5. The Chief Pharmacist is authorized to issue drugs under rules governing the Pharmacy and Therapeutics Committee, subject to the approval of the Medical Advisory Staff.
6. Requests for the approval of new drugs or dosage forms to be available from the Pharmacy are to be submitted in writing to the Secretary of the Pharmacy and Therapeutics Committee (the Chief Pharmacist), who will transmit them to the Committee. Pertinent data are to be made either by the department head or the head of the section desiring the drug; the latter should include the name of the drug and the dosage form required, a statement as to whether the new drug is to replace a drug already in use, and if indicated, a statement describing the advantages possessed by the new drug or dosage form.

(Continued on page 4)



METROPOLITAN HOSPITAL
Pharmacy Bulletin

Volume III — January 31, 1959 — Number 1
Published by the Pharmacy Staff — Editorial assistant Miss B. Ramsay

Newer Pharmaceuticals

ILOSONE - Lilly (erythromycin ester as the propionate) is indicated in the treatment of bacterial infections and, in terms of potency, attains blood concentration levels which are three times as great as the coated tablets of erythromycin. Therapeutic blood levels are attained within 30 minutes after administration and sustained several hours longer than the former preparations of erythromycin.

The usual dose is 250 mg. every six hours. Capsules are available in strengths of 125 and 250 mg.

TRANCOPAL - Winthrop Labs. (chlormethazanone) seems to be of value in disorders characterized by skeletal muscle spasm such as low back pain, neck pain (torticollis), bursitis, rheumatoid arthritis, etc.; in psychogenic disorders including anxiety and tension states, dysmenorrhea, premenstrual tension, asthma and angina pectoris.

For adults the usual dosage is 100 mg. three or four times daily. Tablets are scored and available in a strength of 100 mg. each.

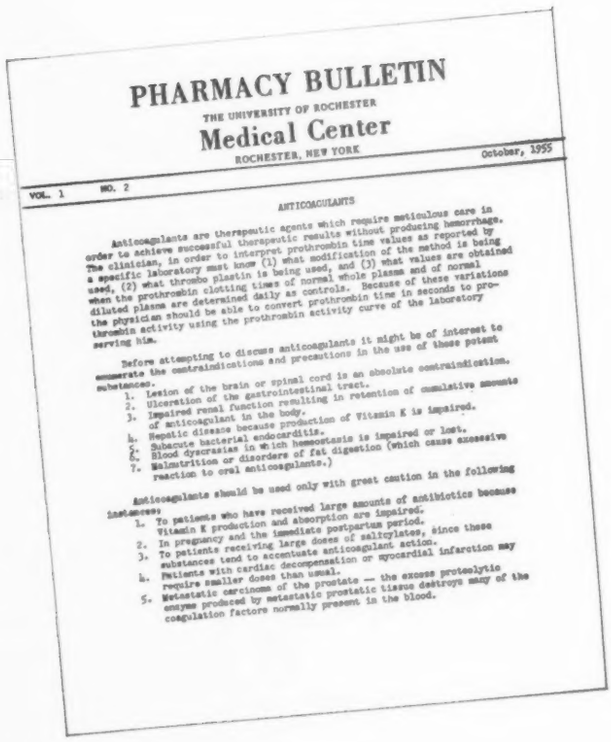
DECADRON or DEXASONIL - Merck, Sharp & Dohme and Schering Corp (dexamethasone) is 16-alpha-methyl-9-alpha-fluoro derivative of prednisolone. The agent is utilized as an anti-inflammatory steroid indicated in a variety of allergic and inflammatory diseases such as rheumatoid arthritis, rheumatoid spondylitis, Still's disease, psoriatic arthritis, periarteritis nodosa, bronchial asthma, allergic rhinitis, etc. Dexamethasone appears to be five times more potent than triamcinolone or methylprednisolone, seven times more potent than prednisone or prednisolone, 28 times more potent than hydrocortisone, and 35 times more potent than cortisone.

Side effects and contraindications are the same as for the other steroids except that it may be the steroid of choice in patients with diabetes because of its virtual freedom from diabetogenic activity.

Dosage can usually be determined on a tablet for tablet replacement basis, i.e., 0.75 mg. will replace 4 mg. triamcinolone or methyl prednisolone, 5 mg. prednisone or prednisolone, 20 mg. hydrocortisone or 25 mg. of cortisone.

Available in scored tablets of 0.5 mg. and 0.75 mg. each.

Page 1



PHARMACY BULLETIN
THE UNIVERSITY OF ROCHESTER
Medical Center
ROCHESTER, NEW YORK
VOL. 1 NO. 2 October, 1955

ANTICOAGULANTS

Anticoagulants are therapeutic agents which require meticulous care in order to achieve successful therapeutic results without producing hemorrhage. The clinician, in order to interpret prothrombin time values as reported by a specific laboratory must know (1) what modification of the method is being used, (2) what thrombo plastin is being used, and (3) what values are obtained when the prothrombin clotting times of normal whole plasma and of normal dilluted plasma are determined daily as controls. Because of these variations the physician should be able to convert prothrombin time in seconds to prothrombin activity using the prothrombin activity curve of the laboratory serving him.

Before attempting to discuss anticoagulants it might be of interest to enumerate the contraindications and precautions in the use of these potent substances.

1. Lesion of the brain or spinal cord is an absolute contraindication.
2. Ulceration of the gastrointestinal tract.
3. Impaired renal function resulting in retention of cumulative amounts of anticoagulant in the body.
4. Hepatic disease because production of Vitamin K is impaired.
5. Subacute bacterial endocarditis.
6. Blood dyscrasias in which hemostasis is impaired or lost.
7. Malnutrition or disorders of fat digestion (which cause excessive reaction to oral anticoagulants.)

Anticoagulants should be used only with great caution in the following instances:

1. To patients who have received large amounts of antibiotics because Vitamin K production and absorption are impaired.
2. In pregnancy and the immediate postpartum period.
3. To patients receiving large doses of salicylates, since these substances tend to accentuate anticoagulant action.
4. Patients with cardiac decompensation or myocardial infarction may require smaller doses than usual.
5. Metastatic carcinoma of the prostate -- the excess proteolytic enzyme produced by metastatic prostatic tissue destroys many of the coagulation factors normally present in the blood.

1945 with a printed letterhead: LUTHER HOSPITAL MEDICAL STAFF BULLETIN, EAU CLAIRE, WISCONSIN. The introduction of this type of bulletin by the management was a step to enlarge the scope of the bulletin to include other departments besides the Pharmacy. The bulletin has been used by the Administration as well as by the X-ray, Laboratory, and Dietetics Departments. With the addition of a new physiotherapist that department was given added emphasis through the use of the medical staff bulletin. When the bulletin is issued by the Pharmacy, "Department of Pharmacy" is printed below the general heading.

In February, 1945, the department informed the medical staff of the manufacture of penicillin lozenges. These were made from unflavored gelatin to which a preservative had been added. Efforts to purchase a mold were unsuccessful, but an aluminum cake pan which had squares etched on the bottom was used as a mold. After the mixture had been chilled in this mold for a few minutes, a knife was used to divide the product into squares. Since penicillin lozenges were not commercially available and there were many indications for their use, the demand for them was immediate. They were manufactured in the Pharmacy until they became commercially available.

One of our bulletins contained a short review of oral protein derivatives. In it we discussed the various commercial products available and classified them as proteins or protein hydrolysates. They were compared as to their amino acid or protein content, the source, calories, price and as to the addition of vitamins. They, in turn, were compared to dry skim milk. This comparison brought out the fact that if protein is indicated, dried skim milk is a good source, palatable, and an inexpensive form.

Another bulletin informed the physician of the availability of Coccidioidin Diagnostic Test. With this test the physician is able to tell if the patient has been exposed to this fungus of the southwestern part of the United States. Since x-ray findings of this fungus are similar to pulmonary tuberculosis and virus pneumonia, the test can be of great value. The bulletin also listed several new products available in the Pharmacy.

Subjects of the other bulletins have been blood fractionation products, including a brief summary of fibrin foam, thrombin topical, dried human blood cells, and immune globulin. Other subjects have been bacitracin, the pharmacy library, antihistamine drugs, convalescent serums, penicillin products, dihydrostreptomycin, vitamin B_{12}, drugs used in the treatment of Parkinson's disease, summary of present arthritic drugs, and availability of cortisone and cumopyran. Another popular subject has been the comparison of various products, such as the potency and cost of

therapeutic vitamins. This will give you some idea of the subjects I have used.

I have copies of several newsletters that you might like to have. I would like to comment on some of the different types of bulletins of which these I am distributing now are examples. I am grateful to the pharmacists in these hospitals for supplying a copy so that they could be reproduced for you.

Metropolitan Hospital Bulletin

The first of these, *Metropolitan Hospital Pharmacy Bulletin,* was supplied by Edward Superstine, Chief Pharmacist of Metropolitan Hospital in Detroit, Michigan. You will notice that it is a mimeographed bulletin, and he has one of his staff as his editorial assistant. This is the first page of a four page release. All the pages are numerically numbered, which makes for convenient reference, especially if an index is made for each year's copies. It is printed on yellow paper which makes it distinctive and easy to read.

After an excellent statement concerning hospital policies, newer pharmaceuticals are described. On the third page of this release is a page, "Did you Know That," in which several interesting facts are listed such as:

"Factors influencing your chances of being a heart disease victim are partly hereditary, but your weight, blood cholesterol level, blood pressure, and amount of cigarette smoking are important." It concludes with a section "Current Comment." There are several pertinent comments from articles in medical journals on the infection from thermometers and on the ingestion of mercury.

LANKENAU HOSPITAL PHARMACY NEWS

Issued to Further Liaison Between the Hospital Pharmacy and the Medical Staff
Your comments and recommendations make "News" of maximum value

Volume II — Valentine Edition 1956 — Number IV

Co-Editors Estelle Fairman, Dispensing Pharmacist
Thomas A. Manzelli, Chief Pharmacist

CARDIOVASCULAR AGENTS

DIGALEN, Not L.N.F. — See Digitoxin For Comparable action
DIGIPOLIN, Not L.N.F. — See Digitoxin For Comparable action
DIGITOPURIN, Not L.N.F. — See Digitoxin For Comparable action
DIGIGLUSIN, Not L.N.F. — See Digitoxin For Comparable action
DIGILANID — See Lanatoside C
DIGITALLINE NATIVELLE — See Digitoxin for Comparable action
DIGISIDIN — See Digitoxin for Comparable action

DIGITALIS U.S.P. (Foxglove) Use: In cardiac decompensation
Note: Watch for early symptoms of overdosage which include anorexia, nausea and vomiting. Digitalizing and maintenance dose must be adjusted to the needs of the individual patient.
Dose: For digitalisation, about 1.0 to 1.5Gm, given as six to eight tablets at once, followed by two to four tablets every six hours until digitalisation is complete.
Rx For Maintenance, 0.1 Gm
Digitalis tablets, U.S.P. 0.1 Gm
Digitalizing and maintenance doses depend on the individual.

DIGITOXIN U.S.P. (Crystodigin, Cardigin, Digisidin, Digitalline Nativelle, Purodigin)
Use: In cardiac decompensation, curicular fibrillation, and other heart disorders, it is rapidly and almost completely absorbed.
Note: Watch for early symptoms of overdosage, which indicate the patient is fully digitalized. These include nausea, vomiting and pulse rate below 60 per minute. The potency of 1 mg of digitoxin is approximately equivalent to 1 Gm of Digitalis. Digitalizing and maintenance dose must be accurately adjusted to the needs of the individual patients.
Free Floor Stock.
Dose: For digitalisation, from 1.2 to 1.5 mg in divided doses of 0.2 mg to 0.5 mg at four to six hour intervals, or 1.2 mg at once with succeeding 0.2 mg doses every four to six hours.
For maintenance, the daily dose is 0.1 mg to 0.2 mg
Rx Digitoxin Injection U.S.P. 0.2 mg per cc, 10cc vial
For intravenous use preferably, irritating by other routes. May be given intramuscularly.
Digitoxin Tablets U.S.P. 0.1 mg (colored red), 0.2 mg (white)
Digitalizing and maintenance doses depend on the individual.

GITOXIN U.S.P.
Use: Cardiac decompensation of low out-put failure.
Note: Caution: Digoxin is extremely poisonous, used for rapid digitalisation with maintenance doses of digitoxin.
Caution: This drug is very rapidly dissipated and the patient may become undigitalized in a day or two.

Lankenau Hospital and Lenox Hill

The *Lankenau Hospital Pharmacy News* of Philadelphia, Pennsylvania, has three co-editors. This again is the first page of a three page release. It lists many new drugs, giving brief descriptions of each. Thomas Manzelli is the Chief Pharmacist who publishes this bulletin. You will note this one has a slogan, "Better Health for Better Health Through Pharmacy."

The *Pharmacy Digest of Lenox Hill Hospital,* New York City, of which President Bogash of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS is the editor, has a printed heading. For me this adds something to the appearance of the bulletin.

This three page news bulletin contains a discussion of plasma volume expanders. The article goes into a detailed description of the product, describes the size flasks available, lists common commercial preparations, and tells the cost to the patient. It is a very informative bulletin dealing with one subject.

The bulletin is published under the heading of "Pharmacy Committee" you will note. This gives a stamp of approval by that committee for whatever information is contained.

PHARMACY DIGEST
LENOX HILL HOSPITAL
NEW YORK CITY
Pharmacy Committee

Vol. 2 — September, 1954 — No. 9

ANTICOAGULANTS - A COMPARISON

Submitted for your attention, on the following page, is a chart concerned with drugs affecting the coagulation of blood.

With the recent introduction of several new anticoagulant agents, both 'Council Accepted' and experimental in nature, it was felt that a Chart was needed by the Pharmacy Department as reference material. After completion, it was felt that perhaps this chart might be of value to you.

Please note that the average doses listed are doses used at Lenox Hill Hospital. Inclusion of brand names does not indicate endorsement by the Committee. Finally, the cost comparisons are those of the Pharmacy Department at this hospital.

Veterans Administration Center
Los Angeles 25, California
January 9, 1959

Formulary Supplement
No. 59-1

COMMITTEE ON THERAPEUTIC AGENTS

I. INTRODUCTION

These periodic bulletins are to inform the professional staff of the findings and recommendations of the Committee on Therapeutic Agents, to disseminate information concerning the newer therapeutic agents, and to acquaint the staff with the therapeutic and pharmacy policy. As supplemental to the Formulary, they should be maintained for reference.

II. NEW DRUGS STANDARDIZED FOR GENERAL USE

1. CHYMOTRYPSIN (Chymar)
   Category: Anti-inflammatory Agent, Systemic.
   Dosage Form: Vials - Aqueous, 5 ml.
   Dose - Usual:0.5 to 1 ml. intramuscularly 1 to 3 times daily until clinical improvement is obtained. In chronic or recurrent inflamation, 0.5 to 1 ml. may be injected intramuscularly once or twice per week.
   Precaution: Do not inject intravenously. Chymar Aqueous is stable for one year. It should be stored in refrigerator. Do not freeze.

2. ERYTHROL TETRANITRATE (Cardilate buccal)
   Category: Cardiovascular-Hypotensive Agent.
   Use: Somewhat slower than that of nitroglycerin, it is not intended for the treatment of acute attacks of angina pectoris. Instead, it is designed for the prophylactic and long-term treatment of patients with frequent or recurrent anginal pain.
   Dosage Form: Sublingually or buccal tablets, 15 mg.
   Dose - Usual: One tablet three times daily after meals.
   Precaution: As with all nitrates care must be exercised in treating patients with glaucoma or cerebral hemmorrhage.
   Limited Use: Due to high cost of this dosage form, it is limited to use only in patients requiring long-term treatment with frequent and recurrent anginal pain. NOT A REPLACEMENT FOR NITROGLYCERIN. Controls require that Dr. Pearce in OMSM, and the Diagnostic Clinic Group for Domiciliary be consulted on initial use.

Arkansas Medical Center

The *University of Arkansas Medical Center Pharmacy Bulletin,* where Doctor William M. Heller is in charge, is another example of a very good release. He tells me that the only change he contemplates making is to put a line on the masthead to the effect that the opinions expressed therein are those of the editor and do not necessarily represent the opinions of anyone else at the medical center. Bill was kind enough to send extra copies of his release so that it could be seen in its entirety. Essentially, the bulletin explains changes in policy, availability of new type containers, and additions to the formulary. One of the releases gives a full page of metric doses with the approximate apothecary equivalents.

Nursing Staff Bulletin

The fifth sample copy is one done by the nursing staff in my hospital. This release has been very well received and includes news that might be of interest to the medical staff.

This release is published by our Superintendent of Nurses, Miss Helen Brunclik. Her policy is not to include anything of a personal nature unless it represents some hospital activity. She has used as topics such items as disaster-tornado victims, national conventions, school of nursing notes, hospital notes, and information for interns and residents.

This bulletin is always distributed on a tinted paper which adds to its distinctiveness.

I have a few sample copies of other bulletins that you might like to see. One is the *Bulletin of the Hospital Pharmacy and the Hospital Pharmacy Committee* of the University of California Medical Center, San Francisco. This is essentially a bulletin of the Pharmacy and Therapeutics Committee. It is very nicely done and much more elaborate than most. It has a very attractive cover which is perforated for filing. It gives the proceedings of the Pharmacy Committee. It also has a section entitled "Notes of Interest," and in this issue, tells about a Japanese antibiotic, anticancer drug, new drugs, Vitamin B_{12} absorption, and lists some newly released drugs, giving the trade name, generic name, company and description. It also lists some new drugs currently under investigation and concludes with a formulary supplement. It consists of nine pages which are numbered.

All of these bulletins are examples of what might be distributed in your hospital. Perhaps each has some feature that you might like to incorporate into a publication of your own.

It has been my purpose to present the things you should consider in a publication of your own. I am convinced of the merits of publishing a pharmacy bulletin. I would urge each of you, if you are not now producing one, to include it in the future plans of your department.

SURVEY OF PHARMACY BULLETINS

► A RECENT SURVEY of 100 hospitals, most of them in the greater than 500-bed capacity, showed that a significant number of hospital pharmacies are publishing bulletins or newsletters for distribution in their institutions. There were approximately 50 replies to the questionnaire that was sent out and, of these, thirteen indicated that they were publishing pharmacy newsletters or bulletins. A copy of the bulletin or newsletter was obtained from each of the hospital pharmacies that indicated publication of such an organ.

This study was undertaken by Miss Gael Driscoll, an undergraduate in pharmacy, at the College of Pharmacy of Wayne State University, Detroit. The survey was developed as a requirement for the course entitled "Directed Study in Hospital Pharmacy."

The survey sought to determine: (1) The extent to which hospital pharmacy bulletins or newsletters are published; (2) Who assists with the preparation of the publication; (3) To whom distribution is directed; (4) Where the bulk of the information is obtained for use in bulletins and newsletters; and (5) What the major problem is in publishing a hospital pharmacy bulletin or newsletter.

Results were obtained from two U.S. Army Hospitals, two Veteran's Administration Hospitals, three University Hospitals and six hospitals of other types.

It was found that, in most cases, hospital pharmacies published their bulletins or newsletters with the assistance of people in the respective departments of pharmacy. Information for publication, to a great extent, appeared to come from manufacturers of pharmaceuticals, pharmaceutical journals and publications, and from members of the medical staff of the various institutions as well as from the reports of Drug Evaluations by the Council on Drugs of the American Medical Association.

Most bulletins and newsletters contained information on newer therapeutic agents and these were published as a new drug came into use. In other cases, the publication was prepared on a monthly basis. Bulletins were distributed, according to the survey, to interns, student nurses, and the nursing and medical staffs of the hospitals.

The question concerning major problems of publication was answered in a very similar and consistent fashion. There is a need for more and sufficient time to perform the task of preparing the bulletin or newsletter for publication. Seven out of the thirteen reports indicated that time was the major factor in publishing the bulletin.

preparation of

OPHTHALMIC SOLUTIONS

by JOHN W. WEBB

► MANY ALKALOIDAL SALTS ARE STABLE IN SOLUTION for six months or more when prepared as outlined by Murphy.[1] Collyria containing these salts need only be manufactured twice a year. From the standpoint of work simplification it is desirable to go through the manufacturing procedure as few times as necessary.

Graduates and other measuring devices should be appropriate in size for the volume to be measured. The finished product should be within a prescribed tolerance of plus or minus 5 percent. Some alkaloidal salts *e.g.,* pilocarpine hydrochloride, may be 95 to 99 percent pure while hydrated salts such as zinc sulfate or scopolamine hydrobromide may effloresce to give more active ingredient, on a weight basis, than the official salt. These potential deviations must be taken into account at the time of weighing and illustrate the need for analytical control.

Need for Sterility

Collyria should be prepared with the same deference paid to injectables. The *Federal Register* No. 11, *18,* 351 (Jan. 16) 1953, has the following statement:

"Liquid preparations for ophthalmic use contaminated with viable micro-organisms have been responsible for serious eye injuries, and, in some cases, complete loss of vision . . . such preparations should be sterile . . .any liquid preparations offered or intended for ophthalmic use which are not sterile, may be regarded as adulterated within the meaning of section 501 (c) of the Federal Food, Drug and Cosmetic Act, and further, may be misbranded within the meaning of section 502 (j) of the act. Liquid ophthalmic preparations packed in multiple-dose containers should (1) contain one or more suitable and harmless substances that will prevent the growth of micro-organisms, or, (2) should be so packaged as to volume and type of container, and so labeled as to duration of use and necessary warnings as will afford adequate protection and minimize the hazard of injury resulting from contamination during use."

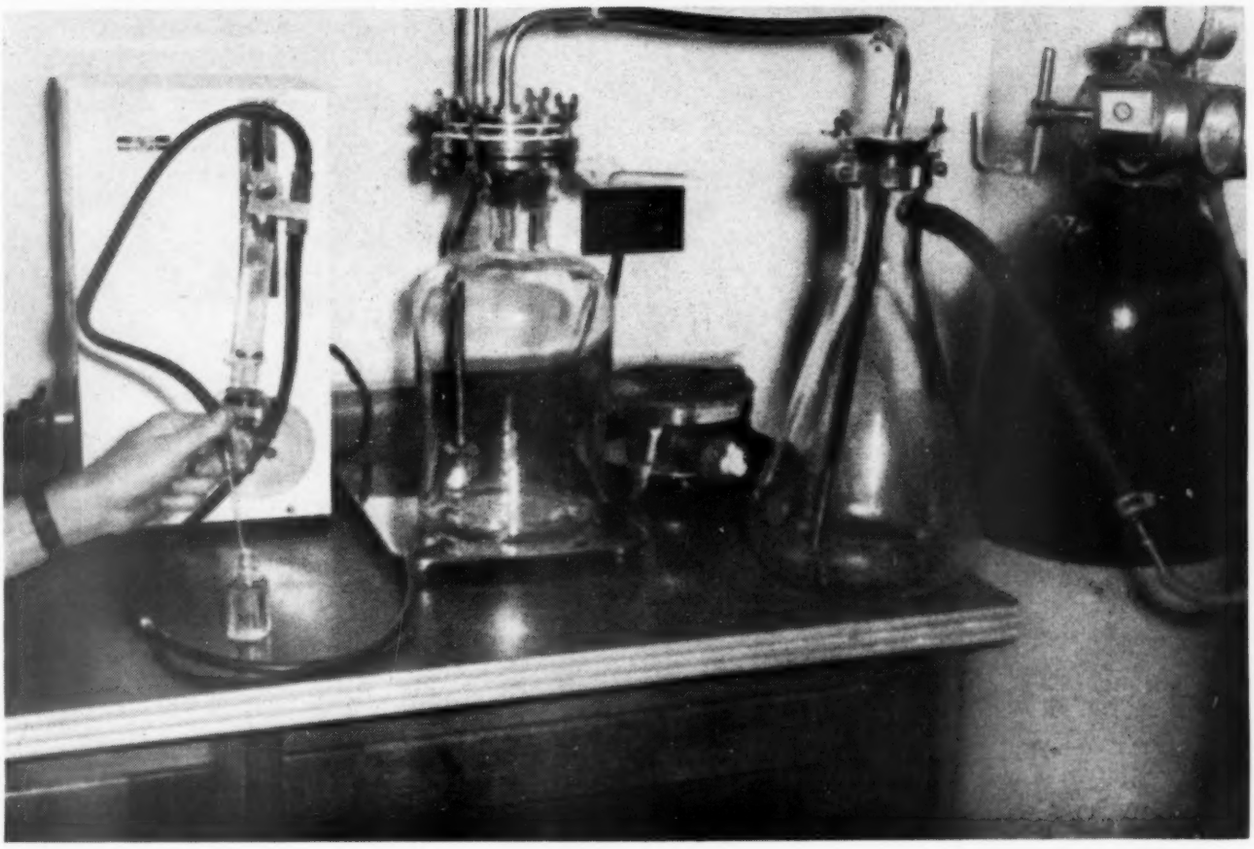
These regulations are directed primarily at the manufacturer, but since few concerns prepare ophthalmic solutions, hospital pharmacists often prepare their own. The responsibility should not be taken lightly. Hospital pharmacists should be particularly careful for they often must dispense collyria that will be put into a damaged eye which no longer has its normal barrier to bacterial invasion. For example, fluorescein sodium solutions are used for outlining damage to the cornea. It is ironical that solutions of fluorescein are among the most difficult to maintain sterile. Serious corneal ulceration can result if *Pseudomonas aeruginosa* is one of the bacterial contaminants.

Hydrogen Ion Concentration

A number of investigators have attempted to determine the *p*H of lacrimal fluid. Hind and Goyan[2] reported the *p*H of tears to be 7.4. At this *p*H the free alkaloid is released from its salt. Swan and

JOHN W. WEBB is Assistant Pharmacist-in-Chief, Massachusetts General Hospital, Boston.

Presented at the Institute on Hospital Pharmacy, Philadelphia, June, 1958.



Ertel filter (positive pressure) with nitrogen, and Brewer automatic pipette

White[3] state that it is the free base that penetrates the cornea. In 1944, Cogan and his co-workers[4] published a series of papers on the permeability of the cornea to weak electrolytes.

While there have been volumes written about buffer systems for collyria, we still recommend avoidance of the use of buffers whenever possible. When a buffer is necessary, one of low buffering capacity should be selected. The *p*H of simple solutions of most alkaloidal salts lies between 4.0 and 5.0. This is the *p*H range where the compounds are usually most stable. Increasing the *p*H, as is often done when buffers are added, decreases stability of the alkaloid and in our opinion is not necessary since tears have a buffering system of their own, capable of bringing alkaloidal solutions to the proper *p*H almost instantaneously. Floyd[5] states: "It appears justifiable to draw the conclusion that vehicles of near-physiologic *p*H are of no decided clinical superiority over more acid vehicles unless the acid vehicle offers a strong resistance to neutralization and is applied in overwhelming quantity . . . under conditions of ordinary clinical practice where the usual dose of a drug solutions is about two drops, even a highly neutralization resistant vehicle does not appreciably interfere with the action of the drug."

The number of ingredients in collyria should be kept to a minimum since the body must metabolize all chemicals introduced into the eye, whether they have any pharmacological action or not.

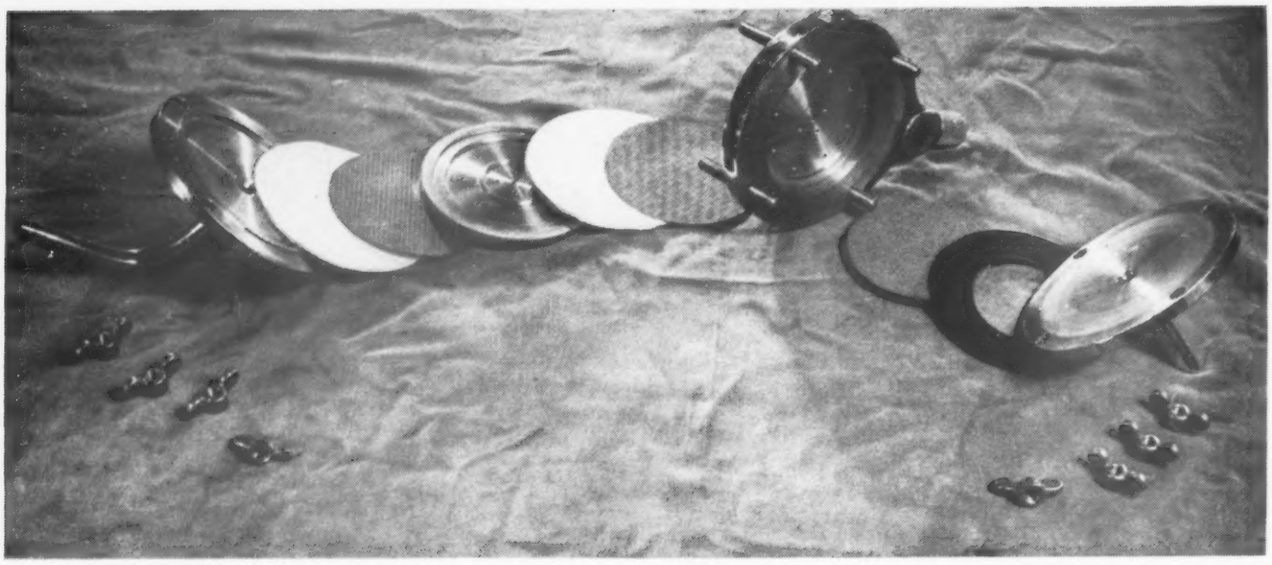
Bacterial Filtration

An effective filter must remove all unwanted elements from the liquid passing through it without changing the essential characteristics of the liquid. Filters with a pore size of 1.5 microns or less will effectively remove bacteria if the solution is not heavily contaminated[6]. Some viruses are removed either by adsorption or by removal of particles that contain viruses.

Although it is recognized that keratoconjunctivitis is a result of viral invasion, we have as yet to have a case reported due to collyria prepared by bacterial filtration. This is probably due to the meticulous care used in their preparation. Freshly distilled water is always used and where it is part of the formula, chlorobutanol is added immediately. The collyria are packaged the same day they are made.

While there are several types of bacterial filters, we use asbestos and fritted glass filters and, accordingly, these will be the only ones described.

Equipment used should be sterilized in an auto-



Ertel filter, disassembled

clave at 121° C. for 20 minutes at 15 pounds pressure per square inch. Dry heat may be used but if rubber is included among the items to be sterilized, dry heat should not be used as an alternate for the autoclave.

All exposed openings of the filter assembly should be wrapped with parchment paper to prevent subsequent contamination.

If pressure is used it is advisable not to exceed fifteen pounds per square inch.

It is recommended that the collection flasks have a tubulure outlet placed on the side near the base. This gives the flask the appearance of an aspirator flask and allows drainage without dismantling the unit. This is important for each time the assembly is dismantled there is a potential break in aseptic technique.

Asbestos Filters

One type of asbestos filter is the Seitz filter[7]. As the liquid passes through the filter, bacteria and other undesirable matter are retained in the interstices of the fiber pad. The filter unit is designed so that each sheet of the asbestos filter is firmly clamped between metal plates. The sealing edges of the plates create a gasket effect around the outer edge of the sheet. The proper size sheet should be used. If the filter pad is too large it will protrude outside the plates and there is a possibility that it may act as a wick to pull in bacteria circulating in the surrounding air.

The filters have a twofold action, *viz.,* mechanical filtration dependent upon pore size plus an adsorptive capacity. There are some pads that will remove anything measuring as little as 0.01 micron. It is claimed that pyrogens can be removed from intravenous solutions with a proper Seitz filter. Normally, for bacterial filtration the S-3 pad is used. A Republic Seitz unit costs about $200.00. If it is stainless steel it costs about $300.00.

It has been said that asbestos filter pads give up Mg[8], Fe, and Ca ions[6] which may cause precipitation of the free alkaloids and inactive drugs such as epinephrine hydrochloride. The amount of free alkaloid that might be precipitated is not significant enough to be demonstrated in our chemical assays. This may be due to the comparatively large volumes passed through the pads for each batch. For the same reason we do not worry about the volume absorbed by the pads unless we are working with small quantities of solution.

Sintered glass filters are used for sensitive items.

Fibers from the asbestos may pass into the filtrate. We circumvent this problem by placing a piece of hard filter paper and a metal mesh under the asbestos pad. Another disc of hard filter paper is also placed over the asbestos pad. Without it there is a tendency for the solution to form channels in the asbestos pad.

While the Seitz filter may be used under pressure, with gravity or with vacuum, we use only vacuum.

One of the advantages of this filter is that the filter pads are thrown away at the end of the operation so that the need for cleaning the bacterial filter itself is eliminated.

The Seitz filter assembly consists of the following parts:

Collection flask with tubulure at base. (Rubber tubing attached to tubulure is clamped off.)

Rubber Stopper (two-hole) fits in collection flask.

Side arm glass filter passes through one hole. The distal end is connected to a cotton filled glass adapter.

Base with wing nut clamps.
Metal mesh.
Filter Paper (hard).
Asbestos pad.
Filter paper (hard).
Top.
Adapter Cap (threaded).

The distal end of the rubber tubing attached to the tubulure is covered with paper secured in place by a rubber band and the entire unit is autoclaved. The tubing is clamped when the assembly is removed from the autoclave. The unit is dried by the heat from the jacket. After the unit has cooled, the clamps, which were held in place by light tension in order to permit steam infiltration, are tightened. If the pads sit loosely in the plates and vacuum is applied, nonsterile air might be sucked into the collection flask. If pressure is used, the solution would leak out until the pads have been wetted and swell sufficiently to form a tight seal. It should be remembered that solutions with a high alcoholic content do not cause swelling as does water so that bacterial filtration is not as effective.

It should be noted that there is also a Seitz filter that is not to be used under pressure.

Another asbestos type filter is the Ertel filter[9]. The laboratory model No. 11 costs approximately $220.00. Four-inch No. 0 pyrogen and bacterial retentive neutral asbestos sheets are used which cost $7.10 per hundred. This assembly is used for solutions that are to be filtered under pressure. Certain substances foam or evaporate when filtered by vacuum, particularly if the filtration rate is slow. Pressure filtration eliminates or reduces this problem.

Compressed gases, such as nitrogen, used as a source of pressure, are sterile because of heat of compression.

The Ertel filter assembly consists of the following parts:

Collection flask with tubulure at base. (Rubber tubing attached is clamped off.)
Rubber stopper (two-hole) fits in collection flask.
Side arm glass filter passes through one hole. This remains open to allow air to pass out from collection flask as fluid comes in.
Bottom tip of Ertel filter passes through second hole.
Base of filter.
Rubber disc (gasket type).
Stone, alumden (3) miotic, mydriatic, miscellaneous.
Ring.
Circular metal sieve.
Asbestos pad.
Ring.
Circular metal sieve.
Asbestos pad.
Top of filter.
Pressure tubing with clamps.
Metal tubing (passes through rubber stopper into unfiltered solution).
Rubber stopper (one-hole).
Clamps with wing nuts (to secure rubber stopper on flask).
Flask with side arm.
Pressure tubing with threaded tip in one end.
Tank of nitrogen.

The liquid to be filtered is transferred through the connection tubing into and through the circulatory passages of the filter. There are *two* filters so that automatically there is double filtration. They are designed so that the two circular filter sheets are placed one above the other, separated by a collecting ring. The liquid must pass through the first sheet, accumulate in the collecting ring between the sheets, and then, as a result of the accumulated pressure, pass through the lower filter sheet. The built-in stone prevents fibers from passing out of the filter.

An adjustable stand permits raising or lowering the height of the filter.

The principles mentioned for the Seitz asbestos pad also apply to the Ertel asbestos pad.

Fritted Glass Filters

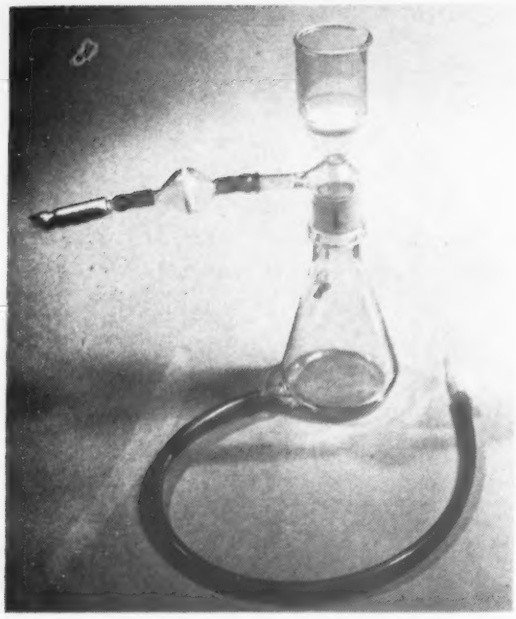
Fritted glass filters have the following features:

They are completely nontoxic, chemically inert, and have no rubber or metal contact.
They are easily autoclaved as a unit.
They are relatively inexpensive.
They must be cleaned after each use.

One type of fritted glass filter consists of a circular fritted glass disc sealed in a Pyrex glass Buchner-shape funnel. This type of filter is available in six different porosities, the ultrafine with a pore size of 0.9 to 1.4 microns being used for bacterial filtration. The Corning company strives to keep the pore size near 0.9 micron. A 150 ml. funnel with an ultrafine frit costs about $20.00.

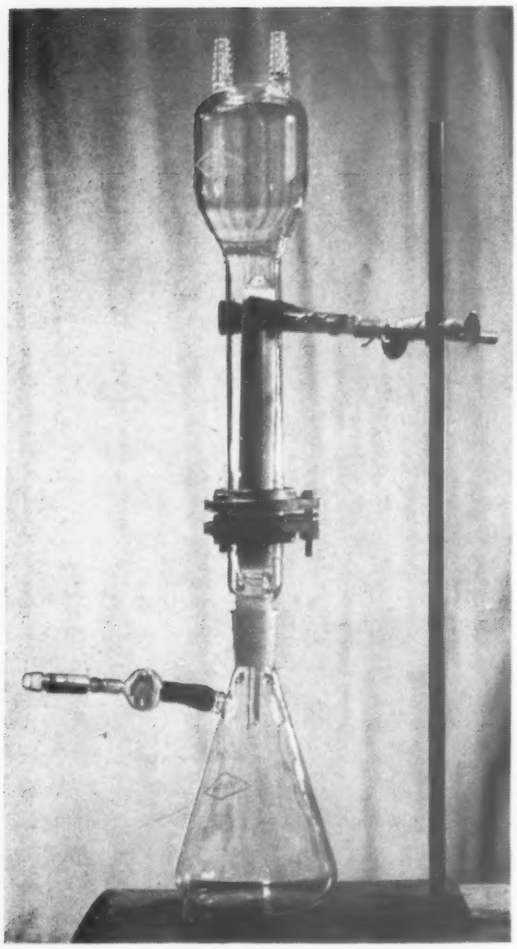
A new fritted glass filter should be washed with suction with hot hydrochloric acid and then rinsed with distilled water before use. To prolong the life of the filter, always clean it as soon as possible after use. Cleaning solutions containing bichromate tend to permanently stain fritted ware, making them undesirable for pharmaceutical work. A good formula for cleaning consists of 5 parts of 90 percent hydrogen peroxide and 95 parts of sulfuric acid. This leaves no metallic residue.

The resistance of fritted ware to thermal shock is less than that of non-porous Pyrex glassware. Therefore, it should not be subjected to excessive temperature nor to direct flame. The temperature commonly used is 121° C. A cold, damp, ultra-fine filter should never be subjected to a sudden temperature change



Morton filter assembly

VirTis Ultrabac Filter



since the evolution of steam may set up sufficient pressure within the filter to crack it. The fritted glass filter assembly consists of:

Collection flask with tubulure near base.

Rubber stopper (two-hole).

Sealing tube with cotton filled glass adapter attached.

Fritted glass filter, ultrafine.

If a large volume is to be filtered, a one-hole rubber stopper may be inserted into the top of the filter and a tubing extended to the mixing vessel.

The sealing tube with reduced ends and a coarse fritted disc has an overall length of 200 mm. and costs about $5.00.

A second type of fritted glass filter is the Morton filter[10]. It is made of Pyrex glass, has an ultrafine fritted glass disc and an inverted standard taper 29/26 ground glass joint. The unit consisting of a 250 ml. flask plus a 60 ml. filter (40 mm. disc) costs about $20.00.

A third type of fritted glass filter is the VirTis Ultrabac Filter[11]. This consists of:

Collection flask with tubulure at base.

Interjoint base device (seats the candle and is inserted into the collection flask).

Fritted glass candle.

Upper reservoir (fits on and around the outer lip of the collection flask and surrounds the candle).

This assembly is all glass and has leak-proof joints. The large surface area insures a high flow rate, but there is also a fairly high retention rate if only a small volume of solution is passed through. For filtering small volumes a Morton filter is preferable. The wall of the collection flask and upper reservoir is made of heavy Pyrex glass which insures resistance to sudden pressure changes.

The reservoir is filled through one of the adapter tips. The second adapter tip is then clamped off. Suction is applied by attachment to a side arm filter connected to the collection flask. If a large volume is prepared, the adapter tip may be connected to a rubber tubing leading to the mixing cylinder.

Bottles

Small bottles, 7.5 ml. capacity, are used because they generally give us a satisfactory volume while allowing us to practice the concept of using small containers to keep contamination to a minimum. For outpatients we also use one ounce bottles for certain preparations, *e.g.,* pilocarpine hydrochloride, that will be used in fairly large quantities in the patient's home. The bottles are put into an automatic vial washing machine, rinsed with cold water, and flushed with hot freshly distilled water. The entire washing cycle takes 75 seconds. The bottles are removed and placed inverted in a drain pan

tilted to allow excess water to flow out through holes in the bottom edge of the pan. The pan, full of inverted bottles, is then placed in an autoclave for 20 minutes at 121° C. and 15 pounds pressure. Then the autoclave is exhausted and the bottles allowed to dry for 20 minutes before removal.

A cover is placed over the pan of inverted bottles and the pan and contents are flipped over so that the bottles are now standing upright in what was the cover. They are placed in a sterile hood[12], bathed in ultraviolet light, and the drain pan removed. This special hood consists of a unit which electrically precipitates dust and bacteria from the air that is being drawn in. The purified air is then pumped across the ultraviolet sterilizer tubes into the filling hood under a pressure that is greater than that of the air in the room. This means that there is always a flow of air *out* of the hood. At the beginning of each work day, the interior of the hood is washed with hexachlorophene in isopropanol. The unit is turned on for at least one-half hour before any filling is done.

The operator scrubs according to the technique of Blank,[13] using sterile cotton gloves after the scrub. To prevent the wetting of the gloves by the solution being bottled, a filling attachment is used.

Bottles are filled one row at a time moving from front to back, each row being capped before moving on to the next row. This eliminates reaching over bottles that are open. The operator should remove watches, rings, and other pieces of jewelry that may harbor bacteria.

The hood mentioned above, costs approximately $1,800.00.

Droppers and Caps

Droppers are included in most bottles of collyria to be used by outpatients but not in those bottles intended for inpatients. The droppers are placed in a rinsing pan and thoroughly flushed with freshly distilled water. The excess water is allowed to drain from the pan before being covered with paper and autoclaved at 121° C. at 15 pounds pressure for 7 minutes. The unit is placed in the hood before the paper cover is removed.

On occasion, we have need for separate sterile droppers. They are prepared by washing with freshly distilled water, placing each in an individual parchment wrapper which is stapled closed and autoclaved at 121° C. for 15 to 20 minutes at 15 pounds pressure. Disposable glass droppers are sterilized in units of twelve. The droppers are placed in a glass screw cap jar which is placed in the autoclave on its side with the cap loose. These are autoclaved for 30 minutes at 121° C. A 4 x 4 piece of gauze separates the bottom of the jar from the droppers.

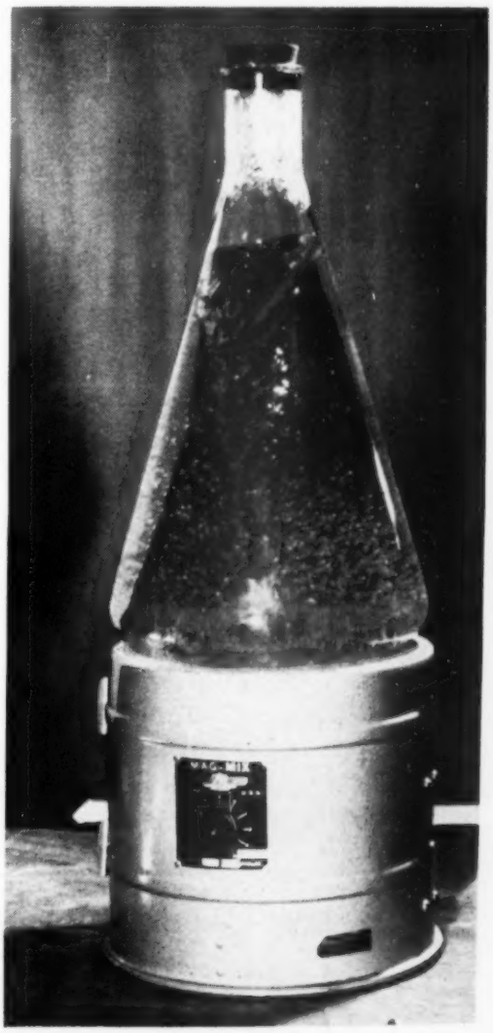
Rubber lined caps of heat resistant plastic are rinsed with freshly distilled water and autoclaved at 121° C. and 15 pounds pressure for 10 to 15 minutes. They are handled aseptically in the same way as the droppers. Rubber lined caps of heat sensitive plastic are placed in a beaker of freshly distilled water and rinsed three times. They are placed in a polyethylene bag and sterilized by ethylene oxide gas with the bag open. After sterilization, the bag is folded two or three times and stapled. If the caps are to be stored any length of time the polyethylene bag is covered with a paper bag which serves as a dust protector. At time of use it is opened in the hood. The technique must be such that the bag can be opened without contaminating the caps.

Vinyl lined caps, instead of rubber lined caps, are used for diisopropylfluorophosphate because of the oil base. They are sterilized by ethylene oxide gas.

Preparation

When a collyrium is to be manufactured certain techniques must be observed. The calibrated mixing vessel (5 gallon glass carboy) with a Teflon coated

Mag-Mix sterile closed system mixing



magnet inside and a rubber stopper is sterilized in an autoclave. Chlorobutanol is added and the vessel is filled to an appropriate volume with freshly distilled water to give a final concentration of 0.5 percent chlorobutanol. The rubber stopper is replaced and the vessel is placed on the motor unit of a magnetic mixer. The rheostat is adjusted to the desired speed and the solution allowed to mix until the chlorobutanol is dissolved. In this way the chlorobutanol is dissolved in a closed sterile system. This solution is then used as the diluent and vehicle for collyria. If a boiling flask is used as a mixing vessel, it is recommended that the calibration mark be made on the neck since this is the narrowest portion of the container and the meniscus can be read with greater accuracy.

After preparation but before filling, an aliquot is sent to the control laboratory for chemical assay. When a satisfactory report is returned, the solution is bacterially filtered and the bottles are filled in the hood. Representative samples are sent to the control laboratory and to the bacteriology laboratory. The goods are quarantined until both laboratories send back favorable reports. This means a minimum wait of ten days. It is desirable to quarantine all collyria after manufacture since some collyria containing an antibacterial agent become sterile after standing 24 to 48 hours.[1]

Collyria which contain pressor amines are filtered through sintered glass. All contain sodium bisulfite. The ophthalmic solution of epinephrine bitartrate N. F. does not have any antioxidant in the formula so the statement is made that the solution must be freshly prepared.

Collyria containing fluorescein sodium is of interest in that the finished solution has a *p*H between 8.0 and 9.0. Sodium bicarbonate is added to help maintain this *p*H. While chlorobutanol is present it is recognized that it is chemically incompatible with fluorescein sodium and will eventually decompose. Nevertheless, its antibacterial action is helpful during the period the preparation is being made and for some time thereafter.

Phenacaine hydrochloride is an alkaloid easily degraded near or above *p*H 7. Chlorobutanol helps insure an acid *p*H and therefore lends stability to this solution.

Collyria containing mannitol, bacteriologically speaking, is normally contaminated with a fair amount of dirt. Therefore, the solution is first filtered through hard filter paper. The filtrate is then passed through an Ertel filter in the regular manner. For the same reason collyria containing methacholine chloride are passed through hard filter paper prior to bacterial filtration.

The preparation of diisopropylfluorophosphate (isoflurophate) in oil is rather involved. First, the persic oil is put into a dry sterile container. An excess of anhydrous sodium sulfate (about 100 grams for each 1,000 ml. of oil) is added. The contents are agitated intermittently for three or four days, then filtered through hard filter paper into dry sterile bottles. The bottles full of oil are sterilized in a dry heat oven. To make sure that the proper temperature for sterilization is reached, leads from a pyrometer are placed in the center of the oil in each bottle. It requires one and one-half hours for approximately 1,000 ml. of oil to reach 140° C. This temperature is then maintained for 4 hours. The bottles are capped and allowed to cool. Approximately 900 ml. of oil is put into a dry sterile mixing cylinder. Approximately a 5 percent solution is made, weighing the isoflurophate by difference in a hood with the exhaust fan on. Additional oil may be measured if necessary. The resulting solution is transferred aseptically to dry bottles and stored until needed. At the time the collyrium is to be made, the 5 percent solution is merely diluted aseptically to the proper concentration and put into an aspirator type flask and from there transferred aseptically in the hood into the 7.5 ml. dispensing bottles.

Collyria containing methylcellulose are impractical to put through a bacterial filter. This is strained through fine cloth and sterilized in an autoclave in the individual 30 ml. bottles for 10 minutes at 121° C. and 15 pounds pressure.

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DRUG SAMPLE CONTROL CABINET

submitted by SAMUEL KOHAN

► A UNIQUE METHOD of controlling unsafe drug sample disposition in the hospital is the utilization of a special drug sample cabinet. This receptacle is placed in the hospital mail room area into which samples, not wanted by the medical staff, are deposited. This receptacle serves as a safe storage place for unwanted drug samples and eliminates the dangerous practice of disposing drug samples into open waste baskets. Thus, lay personnel within the hospital are not able to obtain legend drugs from this source.

The cabinet illustrated on this page measures 45" high, 22" deep and 21½" wide.

Two openings are provided in the sample cabinet. The upper opening is a chute-like arrangement for the deposit of unwanted samples. The lower opening is a door which may be locked and through which the samples may be removed. This type of arrangement of the openings provides a large number of cubic feet in which the samples may be accumulated before the box must be emptied.

This device has provided a useful method of handling unwanted drug samples in one hospital.

The following additional references to the control of drug samples may be of interest to those who have this problem in their hospital.

RIGHT: *Cabinet door opened to remove samples*
BELOW: *top portal lowered for deposit*

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View of Pharmacy Department, St. Francis Hospital, Santa Barbara

ST. FRANCIS HOSPITAL OF SANTA BARBARA

Fifty Years of Service

and the Development of a Small Hospital Pharmacy Service

by SISTER MARY JUNILLA, O.S.F.,

► PLANNING AND DEVELOPMENT OF THE PHARMACY department does not begin with the original founding of St. Francis Hospital fifty years ago. More than half of this operational period was to pass into history before a pharmacy became an actual fact.

SISTER MARY JUNILLA, O.S.F., Ph.G. F.A.C.A., is Chief Pharmacist at St. Francis Hospital of Santa Barbara, Santa Barbara, California

History of Hospital

I was a small child at the time the first rumor was circulated that the Quiesana Hospital on East Arrellaga was soon to change hands. There was a flurry of excitement on learning that this then small resort city was soon going to welcome its first nursing Sisters as residents. The Religious Congregation, I was destined many years later to become a member of, had

completed transfer of deeds to the Quiesana Hospital and were preparing to open its doors, under the name of St. Francis Hospital of Santa Barbara. This bit of history took place in 1908 on August 20. On that day eight Sisters arrived to take over the two story frame building operation. It is ideally situated on the lower shoulders of foothills later to be known as the Riviera.

The sheltered valley in which this city is situated gradually slopes upward ending in a series of foothills which are a part of the coast Range Mountains. Structures erected on them enjoy balcony view of a beautiful valley 100 miles at its longest point and 40 miles at its widest.

This view includes the attractive harbor blending into the deep blue waters of the Santa Barbara channel with its chain of islands rising on the horizon.

Development of Santa Barbara

Santa Barbara was first discovered by Juan Cabrillo a Portuguese navigator in 1542. He found the area inhabited by some 15,000 Yonoli Canalino Indians, possibly of Alaskan origin. It was not until 1769 that Portola's expedition under the Spanish flag found the area. Thirteen years were to pass before Father Junipero Serra O. F. M., founder of the California missions, and a group of Spanish soldiers under Captain Jose de Ortega founded the township. Four years later, its now famous and beautiful mission was built with the help of Indian labor, and Spanish settlers began to arrive. By 1850 the first Yankee and English influx began. Dana's "Two Years Before the Mast," contained a most favorable description of Santa Barbara, which gave impetus to the influx of Yankees. At this time California was under the Mexican flag.

A brief story of the city will probably be valuable and delightful information to those who may never expect to visit here. The city developed from a pueblo, first administered under Spanish rule; then Mexican and eventually American. Santa Barbara at a glance is a clean-looking beautiful city, outwardly effusing wealth, with a predominant and sympathetic Spanish architectural pattern. It was a town of

Aerial view, St. Francis Hospital

4,000 when much of the state was "jack rabbit" paradise, San Francisco an encampment, and Los Angeles only an adobe village of 10,000, in 1880.

Santa Barbara has one of the most civic minded populations of any city in California. It is a highly selective, individual city with a population of 56,000, consisting of wealthy retired citizens and those who make their living from the resort business all the year round. Its two university campuses, ranches, and lemon groves, are some of its attractions. More and more elderly people and families of moderate income are making their homes here. At present it is in the throes of an industrial revolution that is taxing its city planning commission to preserve its program of planned expansion. The city is host to numerous conventions totaling more than 35,370 visitors, some of whom return to live here.

Hospital Expansion

In this atmosphere the hospital grew and expanded. By early 1920, the building was no longer adequate. A new structure was completed in 1923 on a site directly below the former original building which was converted into a nurses residence. The disastrous earthquake of 1925 completely destroyed the new structure along with 85 percent of the business area of the city. Until another building could be financed and built, hospital services were carried on from emergency tents set up on the side of the hill.

Pharmacy Established in 1940

Two years later the first unit of 75 beds was constructed and opened for services. A pharmacy department was not immediately included in the professional service units; however, in 1938 the then incumbent Mother General discussed the economical possibilities with me. At that time three of our Sisters had completed their internship under me at Queen of Angels Hospital in Los Angeles. Sister M. Aquina, O.S.F., after completing her studies at the University of Southern California, was assigned the honor to establish a pharmacy at St. Francis Hospital in 1940. Up to

LEFT: *Schwartz Unit showing tablet section.* ABOVE: *Night cabinet for emergency service*

this period prescriptions had been filled by prescription stores in the area.

Since the hospital serves a growing tri-county area, expansion became necessary by 1954, at which time a four story unit costing close to $1,000,000 was added. This expansion provided additional beds, for a total of 120 or more, a modern surgery, a recovery room with piped in oxygen, a modern therapy pool and treatment rooms, business offices, auditorium and gift shop. Included in the modernization were the kitchen and the pharmacy. For the pharmacy, an additional room wall partition was removed to enlarge floor space, and new cabinets and work benches were installed. These are natural birch with match-formica bench tops. They encircle one and one-half walls, one portion of which is Schwartz sections. A small locked room was made off the desk area and serves as both narcotic and hypnotic storage and dispensing unit. Matching library shelves, files and a desk complete the furnishings. Included in these are a refrigerator and a typing area. There is a small storage unit in the basement.

The pharmacy staff consists of two full-time pharmacists, a part-time pharmacist and a pharmacy helper. The department is open from 8 A.M. to 7 P.M. and one pharmacist is on call for service for after hours in case drugs are needed. However, a well stocked night cabinet supplies most of the needs. It is located in the hallway directly across from the pharmacy entrance. Tablets and capsules are put up in 2, 4, and 6's and replaced in the morning. Requisitions are left on the pharmacy ledge.

An emergency department is directly across the hallway from the pharmacy. Many accident cases are brought in daily. This department requires a comprehensive stock of drugs. A nurse is on duty around the clock and she works closely with the pharmacy department.

Recently a Pharmacy-Nursing Committee was organized. A committee of this type was demonstrated at a recent seminar co-sponsored by the Southern California and San Diego Societies and Pfizer Laboratories. Its objective is to serve as a coordinating body with the nursing service, and its function is to provide a channel for information and for mutual understanding of each others problems and functions. The committee was set up with the cooperation of the administrative and nursing departments. Membership consists of nurses from units with whom the pharmacy has most contact, the director of nurses and special department supervisors and a pharmacy staff member. The chief pharmacist is chairman and one of the members is secretary. She prepares memoranda of proceedings. This material serves for a bulletin which is sent later to each nursing unit.

Service window and pick-up shelves for floor medications

A Therapeutic Committee has been organized with members appointed by the Chief of Staff and the Executive Committee. The medical staff has extended us the privilege of a space in their bi-monthly news letter since we do not issue a department bulletin. This will provide the department with an avenue of contact and informative relationship with staff members.

Since there are no wholesale firms in Santa Barbara all purchases have to be shipped out of Los Angeles or by direct shipment. Representatives call regularly and service is good. Immediately needed drugs are obtained from two or more retail prescription stores in the area. The necessity of pre-planning because of this created a problem at first. However, a downgrading system had to be developed in purchasing and stock volume due to the difference in volume purchasing for a 500 bed hospital from which I was transferred and the 120 bed hospital I now serve.

The Pharmacy is ideally situated, centrally, in the front of the hospital. From our windows we overlook a beautiful city, see its many gardens, and look out over the blue Pacific to the Channel Islands on the horizon. Not only is the view refreshing from the sweeping curve of the coast line and the deep blue ocean, but also the day's heat is tempered by a cool breeze swept in off the channel. Landscaped gardens and orchards surround the St. Francis Hospital between the original building now used as a nurses residence and the present building.

evaluation of

DISPOSABLE PLASTIC SYRINGES

as to physical incompatibilities with parenteral products

by JOHN AUTIAN *and* CHANDRAKANT N. DHORDA

► IT HAS BEEN FOUND THAT THERE IS AN EVER INCREASING DANGER of inducing infectious hepatitis or pyrogenic infections in patients by the reuse of conventional syringes and needles.[1-8] Even though great care is taken in hospitals to clean and sterilize syringes and needles for reuse, there is always the possibility that careless personnel may not have sterilized several of the syringes or needles or that they may have contaminated a few which had been sterilized. There has been a surprising increase in the transmission rate of hepatitis in recent years which may be traced in many instances to the reuse of allegedly "sterile" syringes and needles.

In order to combat this steady rise of cross infections, there have been introduced into medical practice the "disposable" or "one use" syringes and needles. Depending upon the manufacturer, the needles may be separate or affixed permanently to the barrel of the syringe. These disposable units are sterilized and packaged in such a manner as to insure sterility until use.

Other advantages claimed for these disposable syringes and needles are:

1. Reduced physical discomfort to patient by insuring a sharp needle for each injection.
2. Better patient psychology in that the patient realizes that the needles are used only once.
3. Elimination of reprocessing cost for cleaning, sharpening needle point, and sterilizing.
4. Convenience of use.

The present plastic syringes may be composed of polystyrene, polyethylene, polymethyl methacrylate, or nylon. Polystyrene and polymethyl methacrylate syringes resemble in appearance the conventional glass syringes. The polyethylene and nylon syringes are more flexible but not optically clear. Polystyrene, at present, is the most popular plastic for syringes because of its low cost and glass-like appearance.

Even though the literature contains a great deal of information on plastics in general, very little information is available as to the effect a plastic may have upon a drug solution or, conversely, what effect the drug solution may have on the plastic.

At present there is no satisfactory method for predicting which plastic material should be used for one drug or another. This difficulty probably stems from the fact that plastics are high molecular weight, complex organic substances having a variety of chemical structures. Moreover, to make a suitable plastic material, the manufacturers may have complex formulas which, in addition to the polymer, also contain plasticizers, antioxidants, pigments and fillers. Usually, the composition of the plastic is not made available to the user or only parts of the formulation are given. The use of generic names such as polyethylene, polyethylene chloride, polystyrene, etc., are of help in defining the plastic material, but, once again the complete formulation may include other chemical agents which may affect the drug.

Another serious question arises when one considers that even the pure polymers may well contain lower molecular weight polymers and even monomers which may on long contact with the drug solution dissolve into the solvent phase. Whether this would occur at a rate sufficient to be considered alarming would depend upon the solvent system, the length of contact, and the total quantity of polymer and monomer which would be introduced with the drug product into the patient.

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The authors wish to express their sincere appreciation to the numerous pharmaceutical firms which contributed the various parenteral products to this study.

Objectives of Study

This study was undertaken to help answer two questions concerning three plastic syringes. These were:

1. Will a physical incompatibility occur when a parenteral product is kept in contact with the barrel of three types of plastic syringes?
2. Will one or more of several pharmaceutical solvents extract a constituent from the plastic which might cause a toxic or irritational effect upon animals?

No attempt was made to analyze any of the parenteral products to discern if a decrease in potency of the active constituent had occurred. The herculean task of conducting such analysis for several hundred parenteral products was beyond the intent of this investigation.

The three types of plastic syringes* studied were polyethylene, polystyrene and nylon. In each case the syringes were of a 2 ml. capacity with the metal canulas removed. For the sake of uniformity, only the barrels were employed with the canula end fused to prevent leakage. In this paper, only the physical incompatibilities study will be reported.

Physical Incompatibility Studies

Testing Procedure—Each syringe was filled with 2.0 ml. of the parenteral product under study, covered with Parafilm** and placed in an upright position in a specially constructed wooden box. The box was designated to hold eight syringes in a row of each type of plastic or a total of twenty-four syringes. A fourth row of eight openings was used for control samples of solution (2.0 ml.) stored in 10 ml. pyrex test tubes. For each series of eight parenteral products, the box was stored for five hours in the dark room temperature.

At the end of five hours, the content of each syringe was diluted to 10 ml. with freshly prepared distilled water and observed for changes in physical appearance, *p*H*** and for development of haze. The Coleman Model 9 Nephelometer was utilized to detect the formation of haze. If no significant change had occurred as compared to the control samples, the plastic syringe was designated as being compatible with the parenteral product under study. A *p*H variance of less ± 0.3 units and a tolerance of ± 5.0 percent of the Nephelos numbers of the control were considered as not significant.

In these compatibility tests, nephelometric measurements were not conducted on suspensions nor on non-aqueous systems, while hydrogen ion determinations were not performed for nonaqueous systems.

Results

A total of one hundred and twenty-nine official and sixty-two nonofficial injections were tested. The injections* which showed no incompatibility after five hours of contact with the syringes are presented in Table I and II. From the total of one hundred and ninety-two injections, two incompatibilities were noted. A very serious incompatibility occurred with the Paraldehyde Injection and the polystyrene syringe. The paraldehyde dissolved the polystyrene within a relatively short period of time, while no such reaction occurred with either the polyethylene or the nylon barrels.

All the plastic syringes had an effect upon Poliomyelitis Vaccine. The bright pink color of the fresh solution remained the same after five hours of storage in the Pyrex test tube, but this was not the case with the solution in the three plastic syringes. In the syringes, the color had faded to an orange-pink. It should be pointed out, however, that these vaccines contain a dye which changes color when there is a slight alteration in *p*H. Furthermore, this is no indication that a concomitant decrease in potency had occurred.

No deleterious results were observed between the Dimercaprol Injection and the three barrels within the five hour test period. However, after twelve hours of contact, it was noted that the inside surface of the polystyrene had become etched and slightly cloudy. This same result was not observed for the other two types of plastic materials. The Dimercaprol Injection which was tested contained in the formula, besides the active constituent, 20 percent benzyl benzoate and peanut oil. Further investigation of this particular incompatibility indicated that the benzyl benzoate was the substance causing the difficulty.

Mention should also be made that benzaldehyde and benzyl alcohol, depending upon the concentration and length of contact, will have a solvent action upon the polystyrene, but not with either the polyethylene or nylon syringe. Table III summarizes the various incompatibilities.

Discussion

This study indicates the necessity of testing the parenteral products with the various plastic barrels. Even though the number of physical incompatibilities noted was extremely small, these incompatibilities could not have been predicted without the performance of the tests. Furthermore, since no analytical procedures were conducted on the active ingredients, there may be other incompatibilities not discernable by the method of testing reported in this paper. For example, it has been found in the author's laboratory that certain types of plastic materials will bind to various degrees certain types of medicinal agents.

The length of contact the parenteral product has with the various plastic syringes should also be care-

*Plastic syringes supplied by Becton, Dickinson & Company, Rutherford, New Jersey

**Trademarked product of Marathon Corporation, Menasha, Wisconsin.

***Beckman, Model G *p*H meter used for all *p*H determinations.

*In most instances the concentrations were not included in the Tables, but parallel the usual dose/ml. of the solution under study.

TABLE I. OFFICIAL INJECTIONS TESTED AND FOUND PHYSICALLY COMPATIBLE WITH THE THREE TYPES OF PLASTIC BARRELS
(5 Hour Contact at Room Temp.)

U.S.P. INJECTIONS

Adrenal Cortex
Alum Precipitated Diphtheria and Tetanus Toxoids
Aminophylline
Anticoagulant Acid Citrate Dextrose
Ascorbic Acid
Bethanechol Chloride
Bismuth Subsalicylate
Caffeine & Sodium Benzoate
Calcium Gluconate
Chlortetracycline Hydrochloride
Congo Red
Corticotropin
Corticotropin, Repository
Cortisone Acetate Suspension, Sterile
Cyanocobalamin
Deslanoside
Desoxycorticosterone Acetate
Dextrose
Dextrose & Sodium Chloride
Dibucaine Hydrochloride
Digitoxin
Dihydromorphinone Hydrochloride
Dihydrostreptomycin Sulfate
Dimercaprol
Emetine Hydrochloride
Ephedrine Sulfate
Epinephrine
Ergonovine Maleate
Ergotamine Tartrate
Estradiol Benzoate
Estrone
Evans Blue
Folic Acid
Heparin Sodium
Histamine Phosphate
Hyaluronidase
Insulin
Insulin Globin Zinc
Insulin Isophane
Insulin Protamine Zinc
Iodopyracet
Iophendylate
Levarterenol Bitartrate
Liver
Liver Crude
Menadione Sodium Bisulfite
Meperidine Hydrochloride
Mephentermine Sulfate
Meralluride
Mercurophylline
Methadone Hydrochloride
Morphine
Nalorphine Hydrochloride
Neostigmine Methylsulfate
Nicotinamide
Nicotinic Acid
Nikethamide
Ouabain
Oxytetracycline Hydrochloride
Oxytocin
Papaverine Hydrochloride
Parathyroid
Pentylenetetrazol
Phenolsulfonphthalein
Phentolamine Methanesulfonate
Phenylephrine Hydrochloride
Piperocaine Hydrochloride
Posterior Pituitary
Potassic Saline Lactated
Potassium Chloride
Procainamide Hydrochloride
Procaine Hydrochloride
Procaine Hydrochloride & Epinephrine
Progesterone
Protein Hydrolysate
Riboflavin
Ringer's
Sodium Acetrizoate
Sodium Chloride
Sodium Indigotindisulfonate
Sodium Iodomethamate
Sodium Lactate
Sodium Morrhuate
Sterile Mercaptomerin Sodium
Streptomycin Sulfate
Succinylcholine Chloride
Sulfadiazine Sodium
Sulfobromophthalein Sodium
Testosterone Propionate
Tetracaine Hydrochloride
Thiopental Sodium
Tubocurarine Chloride
Vasopressin

N.F. INJECTIONS

Amphetamine Phosphate
Aurothioglucose
Bismuth Potassium Tartrate
Calcium Chloride
Calcium Levulinate
Diethylstilbestrol
Digitalis
Dimethyl Tubocurarine Iodide
Diphtheria and Tetanus Toxoids
Estradiol Aqueous
Gold Sodium Thiomalate
Hexestrol
Lidocaine Hydrochloride
Magnesium Sulfate
Mannitol
Mechlorethamine Hydrochloride
Menadione
Penicillin Procaine in Oil
Pentobarbital Sodium
Phenobarbital Sodium
Picrotoxin
Protamine Sulfate
Quinidine Gluconate
Quinine & Urea Hydrochloride
Quinine Dihydrochloride
Sodium Dehydrocholate
Sodium Iodide
Sodium Para-Aminohippurate
Sodium Psylliate
Sodium Salicylate
Sodium Salicylate & Iodide
Sodium Salicylate & Iodide with Colchicine
Sodium Thiosulfate
Sulfamerazine Sodium
Sulfathiazole Sodium
Vinbarbital Sodium

TABLE II. NONOFFICIAL INJECTIONS TESTED AND FOUND TO BE COMPATIBLE WITH THE THREE TYPES OF PLASTIC BARRELS
(5 Hour Contact at Room Temp.)

Acetazolamide Sodium
Adenosine 5-Phosphate Aqueous
Adenosine 5-Phosphate in Gelatin
Amolanone Hydrochloride
Atropine Sulfate
Azacyclonol Hydrochloride
Casein Hydrolysate
Chlorpromazine Hydrochloride
Cobra Venom
Cobra Venom with Silicic and Formic Acids
Codeine Phosphate
Corpus Luteum
Cyclopentamine Hydrochloride
Darrow's Solution
Diacetylaminotriiodo Benzoate Sodium and Methyl Glucamine
Dibucaine in Oil
Dicyclomine Hydrochloride
Diethylstilbestrol Diphosphate
Diphenhydramine Hydrochloride
Dyclonine Hydrochloride
Erythromycin I.M.
Estradiol Benzoate and Progesterone
Ethyl Iodophenylundecylate
Fructose 5% in Water
Fructose 5% with Electrolytes
Fructose 10% with Electrolytes
Hexylcaine Hydrochloride
Hydralazine Hydrochloride
Hydrocortisone Acetate
Hyoscine Hydrobromide
Invert Sugar in Saline
Iodipamide Sodium
Iodopyracet
Iron-Dextran
Liver-Folic Acid-B12
Lyophilized Crystalline Trypsin
Methamphetamine Hydrochloride
Ovarian Substance
Penicillin G Procaine Crystalline, Dihydrostreptomycin
Polymyxin B Sulfate
Procaine Penicillin G, Buffered Penicillin G Potassium Aqueous
Procaine Penicillin G Aqueous
Procaine Penicillin G in Oil
Prochlorperazine Ethanedisulfonate
Promazine Hydrochloride
Protoveratrines A and B
Pyridoxine Hydrochloride
Pyridoxine-Thiamine
Reagent for Thromboplastin Control and Coagulation
Secobarbital Sodium
Sodium Salt of Diatrizoic Acid
Sodium Diprotizoate
Sodium Folate
Sodium Pteroylitrigluconate
Sodium Benzoate
Testosterone
Theophylline
Thickened Sodium Acetrizoate
Tolazoline Hydrochloride
Tridihexethyl Iodide
Vitamin B Complex (Vit. B_1, B_2, B_6, B_{12}, Sod. Pantothenate, Niacinamide Ascorbic Acid and Folic Acid)
Viomycin Sulfate

fully considered. In these studies, the contact time was limited to five hours, since it was felt that the actual use of this type of syringe from filling the syringe to injection would not exceed five hours. Longer periods of contact may not produce negative results and may be illustrated by referring to Dimercaprol Injection which had a deleterious effect upon the polystyrene syringe after twelve hours of contact. No such result was detected in the five hour period.

Of equal importance to the length of contact is the consideration, if an incompatibility occurred, of the other ingredients in the parenteral product. For

TABLE III. INJECTIONS OR SOLUTIONS FOUND INCOMPATIBLE WITH PLASTIC BARRELS

INJECTION OR SOLUTION	CONTACT TIME WITH BARRELS	RESULTS
Paraldehyde Injection	up to 5 hours	dissolves polystyrene but no effect on polyethylene or nylon.
Poliomyelitis Vaccine*	up to 5 hours	change in color of solution with all three types of syringes.
Dimercaprol Injection**	up to 5 hours	no effect on any of the three types of syringes.
	after 12 hours	etching and clouding of internal surface of polystyrene but no effect upon polyethylene or nylon.
Benzyl Alcohol	up to 5 hours	dissolves polystyrene but no effect upon polyethylene or nylon.
Benzaldehyde	up to 5 hours	dissolves polystyrene but no effect upon polyethylene or nylon.
Benzyl Benzoate	up to 5 hours	dissolves polystyrene but no effect upon polyethylene or nylon.

*Color change due to slight alteration in pH.
**The solvent effect was due to the benzyl benzoate in the injection.

example, even though Dimercaprol Injection gave an incompatibility, the ingredient causing the incompatibility was the benzyl benzoate. In another study,[9] it was reported that Erythromycin I.M. Injection had dissolved a plastic-hubbed hypodermic needle. It was found, however, that the particular injection utilized in the test contained the solvent, diethyl carbonate, and this agent was responsible for the incompatibility. In the study of the plastic syringes, no incompatibilities were noted with the Erythromycin Injection and the three types of plastic barrels.

Benzyl alcohol may produce an incompatibility with polystyrene if the concentration and time of contact are optimum. No such incompatibility was noted with several of the parenteral products which contained benzyl alcohol as a preservative in the five hour test period. Benzaldehyde was included in the study because of its relationship to the benzyl alcohol and benzyl benzoate.

In the evaluation of the three types of plastic barrels, the polyethylene and nylon syringes proved to be the most inert when physical incompatibilities were considered. Polystyrene caused two incompatibilities from a total of one hundred and ninety-two injections tested.

Summary and Conclusion

1. One hundred and twenty-nine official and sixty-two nonofficial injections were tested for any physical incompatibility with the three types of plastic barrels. Several incompatibilities were noted. They were:

a. Poliomyelitis Vaccine developed a color change with each of the plastic barrels.

b. Paraldehyde Injection dissolved the polystyrene barrel, but had no effect on the polyethylene or nylon.

c. Dimercaprol Injection etched and produced a cloudy internal surface (after twelve hours of contact) with the polystyrene barrel, but not with the other two types. No such result was noted within the five hour study period. Benzyl benzoate was found to be responsible for this reaction.

2. It should be noted that the compatibility studies were performed for a period of five hours at room temperature and the results may not necessarily be applicable to longer periods of contact or with other plastic formulations having the same generic names. Since no analyses were conducted on the active ingredient in the parenteral products, other incompatibilities may have occurred which could not be detected by the testing methods reported in this paper.

3. It must be noted that glass control studies have shown no incompatibilities.

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Therapeutic Trends

edited by WILLIAM JOHNSON

Bephenium Hydroxynaphthoate—Anthelmintic

Bephenium hydroxynaphthoate, a new drug, was compared with tetrachlorethylene in the treatment of 284 cases of hookworm infection in Ceylon. Results of the clinical trials were stated in *Brit. Med. J.* 2:1572 (Dec. 27) 1958 by Goodwin, *et. al.* The hydroxynaphthoate was selected as the most suitable salt. Dosages of two or three grams of base compared favorably with tetrachloroethylene. The drug was especially suitable for use in patients with advanced anemia, diarrhea, and heavy hookworm infection because of its low toxicity and because no purge was needed. Another advantage of bephenium hydroxynaphthoate over tetrachloroethylene is its effect against roundworm infections which frequently accompany hookwork infection.

RICHARD H. HARRISON

Amopyroquin—Antimalarial Compound

Laboratory studies indicate that 37 times as much quinine as amopyroquin was required for 90 percent suppression against blood induced *Plasmodium lopharae* infections. A fluorimetric procedure for assaying the drug in biological material was devised. Application of this procedure showed that following oral administration to rats, amopyroquin, an analogue of amodiaquin, was absorbed rapidly, concentrated in the tissues (particularly in the liver, spleen, lungs, and kidneys), and was degraded or excreted slowly. Dogs tolerated well oral doses of 33 mg./Kg., twice daily, five days a week for three months. Rhesus monkeys tolerated 5 mg./Kg. intravenously. Intramuscular irritation tests showed that 2.5 or 3.0 percent solution caused slight to considerable injury in dogs and slight to moderate injury in monkeys. Histopathology associated with the chronic administration of large amounts of the drug was assessed in rats and dogs. The villi of the small intestine of rats showed subepithelial vacuolation and/or a marked accumulation of macrophages filled with a material suspected to be the drug. Similarly filled macrophage aggregates also were induced in the intestinal and mesenteric lymphoid tissue and in the lungs of rats. Dogs exhibited vacuolation of the parenchymatous cells of the liver as well as the changes seen in rats. However, no evidence of a drug cytotoxic effect could be detected in either rats or dogs. This report by Paul E. Thompson *et al* appeared in *Antibiot. Chemotherap.* 8:450 (Sept.) 1958. The Parke Davis and Company trade name for amopyroquin is Propoquin.

WILLARD E. HERSHBERGER

Debricin—A New Proteolytic Enzyme

Debricin, a new enzymatic agent in surgical wounds, was developed from the ficin latex of the fig tree. This powdered material is mixed with a buffer, and it is activated by mixing the enzyme with a special jelly base or 100 ml. of normal saline. Debricin has been evaluated in a variety of surgical lesions in 139 patients. There was rapid, complete debridement when the enzyme was properly used on various types of ulcerations, deep burns, sinus tracts, and wound infections. Debricin used topically is nontoxic and there has been no evidence of systemic toxicity and very little evidence of wound maceration. Parenteral and possibly topically applied antibiotics should also be utilized during the course of surgical wound therapy. The new proteolytic enzyme improved the conditions for healing by its cleansing ability. Its use should be followed by the appropriate surgical procedure to obtain wound closure when indicated. Further studies on local enzyme-antibiotic combinations are in progress as related by Cornell *et al* in *Surg. Gynec. Obst.* 108:93 (Jan.) 1959.

SYLVIA SCHMIDT

Dichloro Analogue Of Isoproterenol

DCI, a dichloro analogue of isoproterenol (β-hydroxy-N-isopropyl-3,4-di-chlorophenethylamine hydrochloride; Lilly 20522), is found to selectively block the cardiac positive inotropic and chronotropic effects of adrenergic stimuli in dogs with intact circulatory systems and in isolated hearts of rabbits. In dogs, no inhibition of the positive inotropic effects of

digoxin, theophylline or calcium chloride was observed. In isolated rabbit hearts, DCI has qualitatively the same blocking action on these effects of theamine but not on those of calcium, theophylline or ouabain. The dichloro analogues of epinephrine (DCE) and norepinephrine (DCNE) have similar blocking actions to those of DCI but are less potent. In both the dog and rabbit heart, DCI initially stimulates and with subsequent doses depresses the heart. DCNE has similar effects in the dog, but in the rabbit heart it, like DCE, produces only depression. Moran and Perkins in *J. Pharmacol. 124*:223 state further that cardiac depressant effects are not antagonized by atropine. The vasopressor effect of epinephrine in dogs is potentiated by DCI, while the effect of isoproterenol is completely blocked, but not reversed by DCI. On intravenous administration, DCI transiently lowers blood pressure, while DCNE produces a prolonged rise. DCI, Lilly 20522, was supplied by Lilly Research Laboratories.

SYLVIA SCHMIDT

Pempidine—Hypotensive

Pempidine 1,2,2,6,6,-pentamethylpiperidine, a new ganglionic blocking drug, is effective in the therapy of hypertension as reported in *Lancet 2*:6 (July) 1958. Harington *et al* (London) studied the pharmacology of this compound and used it clinically in 27 hypertensive patients. Pempidine resembles mecamylamine in that it is very well absorbed after oral administration. However, the excretion of pempidine is more rapid and less affected by variations in acid-base balance. Treatment of hypertension with pempidine was usually started, using 2.5 mg. every 5 hours during the waking hours. The amount administered could be raised rapidly by increasing each dose by 2.5 mg. daily until a satisfactory reduction in blood pressure was achieved. The average daily maintenance dosage was 16 mg. The patients in this series were under treatment for an average of 10 weeks and were continuing on pempidine. Side effects were common, but of only mild or moderate degree. Constipation occurred most frequently (18 out of 27 patients), together with dryness of the mouth (18), and blurring of vision (12). All complaints disappeared rapidly, in 6 to 12 hours, on discontinuing the drug. May & Baker, Ltd. trade name for pempidine is Perolysen.

WILLARD E. HERSHBERGER

New Morphine Derivatives

Five new morphine derivatives were studied in mice with regard to analgesia, acute toxicity, and gastrointestinal inhibition. Results with mice indicate that saturation of the C-ring of the morphine molecule combined with methylene or methyl substitution at C_6 increases analgetic potency more than toxicity. Thus, 6-methyl-7-hydroxydihydrodesoxymorphine, 6-methylenedihydrodesoxymorphine, and 6-methyldihydrodesoxymorphine are 16 to 80 times more potent than morphine and possess therapeutic indices 5 to 22 times as great. Morphinone is less potent and has a lower therapeutic index. Okun and Elliott relate in *J. Pharmacol. 124*:255 (Nov.) 1958 that all compounds caused less gastrointestinal motility inhibition in mice, but their action was of shorter duration than morphine. The most promising derivative, 6-methylenedihydrodesoxymorphine, was found to cause analgesia in doses which had minimal side effects. These drugs may be useful for preanesthetic medication or as constituents of balanced anesthesia. However, if their duration of action is too short in man, they will not be useful for control of pain unless the side effects are truly minimal.

SYLVIA SCHMIDT

NA 2-EDTA

John G. Rukavina *et al* describes in *J. Invest. Dermatol. 31*:259 (Nov.) 1958 the effects of an intravenous chelating agent, NA 2-EDTA. Three patients with proven cutaneous and suggestive visceral sarcoidosis have been treated experimentally with this potent oligometal binding agent (NA 2-EDTA). There was clinical and histologic evidence of improvement in all cases. Further experimental endeavors with this new therapeutic agent are now in progress. NA 2-EDTA was supplied by Abbott Research Laboratories as Edathamil Disodium.

WILLARD E. HERSHBERGER

Sodium Polyhydroxyaluminum Monocarbonate Hexitol Complex

In vitro studies of sodium polyhydroxyaluminum monocarbonate hexitol complex as a gastric antacid conducted by Gwilt *et al* were described in *J. Pharm. Pharmacol. 10*:770 (Dec.) 1958. Several common antacids were tested in addition to the sodium polyhydroxyaluminum monocarbonate hexitol complex. The techniques used were similar to those of previous workers. The new complex compares well with the best preparation tested, a liquid aluminum hydroxide gel, in rate and amount of acid neutralized and in maintenance of the *p*H at optimum range of 3.5 to 4.5. Drying and tableting seem to reduce the activity of aluminum hydroxide gels, while they have no effect on the new hexitol complex. Results show the new compound to be at least twice as fast in action as the best dried gel tested. It also has superior powers of neutralization and *p*H maintenance. This drug appears to have great potential in clinical use in the convenient form of tablets.

RICHARD H. HARRISON

Timely Drugs

Abminthic

CHEMICAL NAME: Dithiazanine iodide.

INDICATIONS: Cyanine dye possessing polyhelminthic activity against giant roundworm (Ascaris lumbricoides), American hookworm (Necator americanus), threadworm (Strongyloides stercoralis), whipworm (Trichuria trichiura), and pinworm (Enterobius vermicularis).

SIDE EFFECTS AND CONTRAINDICATIONS: Occasionally, vomiting and diarrhea; should not be administered in presence of signs suggestive of intestinal obstruction or of acute abdominal disease.

DOSAGE: Adult, 200 mg. three times daily for 5 days for pinworm, giant roundworm and whipworm; for threadworm, 10 to 14 days; for hookworm, 600 mg. with 2 Gm. tetrachloroethylene daily on 3 successive days. Children, up to 60 pounds, 10 mg. per pound daily, in divided doses, not exceeding a daily total of 600 mg.

PREPARATIONS: Enteric coated tablets of 200 mg.

PACKAGING: Bottles of 100 tablets.

SUPPLIER: Pfizer Laboratories.

Daricon

CHEMICAL NAME: Oxyphencyclimine hydrochloride.

INDICATIONS: Anticholinergic compound of value in peptic ulcer, functional bowel syndrome, biliary tract disease, hiatus hernia accompanied by esophagitis, gastritis or ulcer, gastritis, duodenitis, bladder spasm, etc.

SIDE EFFECTS AND CONTRAINDICATIONS: Dryness of the mouth is most common; occasionally, blurring of vision, constipation, and urinary hesitancy or retention. Caution should be used in patients with prostatic hypertrophy or glaucoma.

DOSAGE: Adult, 10 mg. twice daily; children, 0.2 mg. per Kg. per dose.

PREPARATIONS: Tablets of 10 mg.

PACKAGING: Bottles of 60 and 500 tablets.

SUPPLIER: Pfizer Laboratories.

Dilaudid Cough Syrup

COMPOSITION: Dihydromorphinone (Dilaudid) hydrochloride and glyceryl guaiacolate.

INDICATIONS: In treatment of persistent cough regardless of etiology, acute bronchitis and tracheitis, and other forms of bronchial irritation.

SIDE EFFECTS AND CONTRAINDICATIONS: May be habit forming and subject to Federal narcotic regulations.

DOSAGE: One teaspoonful repeated in three to four hours.

PREPARATIONS: Peach-flavored syrup containing in each 5 ml.: dihydromorphinone hydrochloride 1 mg. and glyceryl guaiacolate 100 mg.

PACKAGING: Bottles of 1 pint.

SUPPLIER: Knoll Pharmaceutical Co.

Doxical

CHEMICAL NAME: Calcium bis-(dioctyl sulfosuccinate).

INDICATIONS: Fecal softener in constipation; related to dioctyl sodium sulfosuccinate, but is a double molecule; has double the surfactant action and is physiologically inert.

DOSAGE: Adults, 240 mg. once daily; children over 6, 50 to 150 mg. once daily.

PREPARATIONS: Capsules of 50 mg. and 240 mg.

PACKAGING: Capsules of 240 mg., bottles of 15 and 100 red capsules; 50 mg., bottles of 30 and 100 pink capsules.

SUPPLIER: Lloyd Brothers, Inc.

Enarax

COMPOSITION: Oxyphencyclimine hydrochloride and hydroxyzine (Atarax) hydrochloride.

INDICATIONS: In treatment of multiple gastrointestinal symptoms; provides relief in peptic ulcer, functional bowel syndrome, ulcerative colitis, biliary tract dysfunction, gastritis, etc.

SIDE EFFECTS AND CONTRAINDICATIONS: Mouth dryness, blurring of vision, dizziness, and urinary hesitancy; use with caution in patients with prostatic hypertrophy or glaucoma.

DOSAGE: One-half to one table twice daily, preferably in morning and before retiring.

PREPARATIONS: Tablets containing oxyphencyclimine hydrochloride 20 mg. and hydroxyzine hydrochloride 25 mg.

PACKAGING: Bottles of 60 tablets.

SUPPLIER: Roerig.

Teenac

COMPOSITIONS: Mercuric sulfide, red, and colloidal sulfur.

INDICATIONS: Adjunctive therapy in treatment and control of acne; also of benefit in superficial infections such as impetigo, heat rash, secondary infection of diaper dermatitis, pustular folliculitis or where drying of the skin is desirable.

SIDE EFFECTS AND CONTRAINDICATIONS: Use should be avoided in patients known to be sensitive to mercury compounds.

DOSAGE: Apply lightly, do not rub in.

PREPARATIONS: Grease-free thixotropic base containing red mercuric sulfide 0.5%, colloidal sulfur 1.5%, and urea.

PACKAGING: Tubes of ½ and 1½ ounce.

SUPPLIER: Paul B. Elder Co.

Zinc Gelatin U.S.P. (Unna's Gelatin Paste)

INDICATIONS: As protective and supporting dressing for varicose veins, eczema, and ulcers.

DOSAGE: Liquefy zinc gelatin on water bath and apply on gauze in 3 layers; keep in place for 3 days to 2 weeks; remove by applying water at 95 to 98° F.

PACKAGING: Jars of one pound.

SUPPLIER: Archer-Taylor Co.

Consulting WITH BOWLES

GROVER C. BOWLES JR., *Baptist Memorial Hospital, Memphis, Tennessee*

► We will appreciate any suggestions you may have about the care of stainless steel sinks, tanks and other equipment fabricated from stainless steel.

Soap and water or detergent and water are usually sufficient for the routine cleaning of stainless steel counter tops, mixing tanks, refrigerators and other equipment. Use warm water and plenty of soap. To prevent water spots, rinse thoroughly with warm water and wipe dry with a soft, clean cloth. Spots and stains that cannot be removed by this method can frequently be removed with a paste made by mixing water with one of the mild household abrasives. When applying abrasives, always rub in the direction of the polish lines on the steel to preserve the original finish.

"Heat tint," the slightly darkened areas which develop around ovens and hot plates can generally be removed with stainless steel wool and paste made with water and one of the mild household abrasives. Always rub in the direction of the polish line.

Heavy deposits of petrolatum and wax may be removed from stainless steel by scraping with plastic, stainless steel or wooden spatulas. Rust stains may result from scrapings stainless steel with ordinary steel spatulas or knives.

Chlorine containing solutions tend to damage stainless steel if left in contact for more than a few hours and chemicals such as sodium chloride, iodine, etc., should be removed immediately to avoid staining and pitting of the stainless steel.

► Should income from parenteral fluids such as dextrose and saline be allocated to the Pharmacy Department?

Generally speaking, income from parenteral fluids is allocated to the Pharmacy Department. However, this may vary from hospital to hospital depending upon administrative policy. If solutions are prepared by the pharmacy or if they are purchased, stored and dispensed by the pharmacy, it would seem logical that the income from parenteral fluids would be credited to Pharmacy.

► Where can we obtain Celons?

Celons are available from the Celon Company, Muscatine, Iowa.

► What system do you recommend for arranging the drug stock in a hospital pharmacy?

In small departments, I prefer an alphabetical arrangement. All pharmaceuticals purchased, with the exception of certain poisons, are arranged alphabetically regardless of the dosage form. If drugs are prescribed by generic name, then generic nomenclatures should be used. However, if trade names are specified then stocks would ordinarily be arranged alphabetically by trade name.

In larger departments where quantity purchases are made, I prefer to arrange the active inventory by manufacturer and then alphabetically by trade name within each company.

Both arrangements suggested do away with the time honored method of grouping pharmaceuticals by dosage forms such as tinctures, fluid extracts, ointments, tablets, capsules, ampuls, etc.

► Are newsletters or bulletins published by the hospital pharmacy really worth the effort required to produce them?

Yes, I believe newsletters or bulletins for distribution to the professional staff including nursing are definitely worth the time and effort required to publish them. Actually it is possible to prepare concise, factual and informative newsletters without great difficulty. Granted some of the work may have to be done at home in the evening or on week-ends but the rewards are many. You will find that your newsletter is read and that it can be used as an effective means of communication.

► What type of fire extinguishers should be available in the Pharmacy Department?

The portable carbon dioxide fire extinguisher is the most versatile unit for use in the pharmacy. The cost of the carbon dioxide extinguisher is not prohibitive and no installation is required.

Carbon dioxide is effective against fires caused by burning liquids such as alcohol, oils, grease, and electrical fires (motors, appliances, switches, etc.) where a non-conducting agent must be used. Carbon dioxide provides a smothering action for quick extinguishment, leaves no residue, has no ill-effects on food and will not ordinarily damage electrical equipment.

The maximum efficiency of any portable fire extinguisher is during the first five minutes of the fire. Fire extinguishers should be located strategically throughout the Pharmacy Department and should be checked periodically to be sure that they are in working order. All personnel should be instructed in the use of the fire extinguishers available and the proper method of reporting fires in the hospital.

News

ACA Meeting

The American College of Apothecaries will hold its Annual Convention at the Hotel Roosevelt in New Orleans, Louisiana on May 17, 18 and 19, 1959, according to an announcement by President Gerald L. Nutter of Bartlesville, Oklahoma. All pharmacists are invited to attend this meeting and a program designed to assist the practicing pharmacist has been planned.

Lectures on Radioisotopes

A series of four lectures on radioisotopes was recently held at the Veterans Administration Hospital in St. Louis, Missouri, under the auspices of the Residence Training Program for Hospital Pharmacy of the St. Louis College of Pharmacy. The preceptor of this program was Mr. Norman E. Hammelmann, Chief Pharmacist, Veterans Hospital. The lectures were given by Dr. Robert E. Mack who is Chief of Medicine and Director of Radioisotope Research at the Veterans Hospital in St. Louis. He is also Assistant Professor of Medicine at St. Louis University Medical School.

Film Available

"No Margin For Error," is the title of a film recently released by the American Medical Association and the American Hospital Association. This is one in a series of medicolegal films produced by The Wm. S. Merrell Company, pharmaceutical maufacturers.

"No Margin For Error" presents one of the most pressing current problems in legal medicine, the cause and effect of human mistakes in the complex system of the modern hospital. Skillfully and candidly, case histories deal with major causes of in-hospital professional liability action.

Mix-up in patient identification, mistakes in blood bank procedure, and error in medication dosage are examples of problems the film reveals. It reports, based upon a recent study, that 45 percent of all medication errors occur as a result of mistakes in patient identification.

The importance of the operating room sponge count procedure is demonstrated. One sees how 60 to 90 seconds can often make the difference between a correct count or a mistake and possibly legal action.

"No Margin For Error" points the way for active, thoughtful cooperation between medical and administrative staffs of the hospital. Through this film the A.M.A. and A.H.A. show how a large number of incidents caused by human error can be effectively reduced.

"No Margin For Error" is a 16 mm. black and white optical sound film, running time, 30 minutes. Prints are available for loan from The Wm. S. Merrell Company, Cincinnati 15, Ohio, the American Medical Association or the American Hospital Association.

F.I.P. Resolution Concerning Labeling of Toxic Substances

The following resolution concerning the labeling of toxic substances was adopted by the General Assembly of the International Pharmaceutical Federation upon the recommendation of the Section of Industrial Pharmacists. A copy of the resolution has been forwarded to the World Health Organization.

"Whereas there are, in the different countries, wide divergences in the regulations governing poisons intended for therapeutic use—divergences which tend to cause serious complications in the supply of medicaments to the public; and

"Whereas the World Health Organization is already engaged in preparing and establishing useful specifications, such as those of the International Pharmacopoeia, for the purpose of facilitating on the international plane the examination, analysis and the dispensing of medicaments;

"(a) The International Pharmaceutical Federation expresses the wish that the W.H.O. will be able, as suggested by a study group of W.H.O. set up to examine the use of specifications for pharmaceutical preparations, to undertake a study with the object of obtaining uniformity in the principles of classification of toxic substances used in therapeutics in the different countries.

"In particular, it would be advantageous to study the possibility of establishing a list of toxic substances used in therapeutics in respect of which proposals on labeling and supply to the public might be made to the Governments of the different countries.

"(b) The International Pharmaceutical Federation offers to collaborate in these tasks and to make available its experience of questions concerning the supply of pharmaceutical preparations."

► ED CROUMEY, Chief Pharmacist at the Mary Fletcher Hospital in Burlington, Vermont, is currently serving as Chairman of the Committee on Inter-Professional Relations of the Vermont Pharmaceutical Association. Mr. Croumey has been a leader in the New England area and has also taken an active role in the national organizations.

► WALTER F. HITZELBERGER, Director of Pharmacy Service at the Los Angeles County General Hospital, Los Angeles, California, was recently honored by the

Philadelphia College of Pharmacy and Science from which he was graduated in 1912. Mr. Hitzelberger was awarded an honorary degree Master in Pharmacy at the Founders' Day Convocation on February 19. Another graduate of the College, Mr. John F. Hinkle, a practicing pharmacist from Columbia, Pennsylvania, was also presented an honorary degree at the same meeting.

Wegemer Honored

Mr. Norbert Wegemer, Chief Pharmacist at Little Traverse Hospital, Petoskey, Michigan, was recently honored by the Michigan State Pharmaceutical Association. On being made a life member of the Michigan Association, Mr. Wegemer was singled out for his many years of work in pharmacy and for the association.

International Congress of the Pharmaceutical Sciences

The Scientific Section of the International Pharmaceutical Congress will meet for the Nineteenth International Congress of the Pharmaceutical Sciences in Zurich, Switzerland, September 6 to 10, 1959. Program plans have been announced by Professor Dr. K. Steiger-Trippi, Secretary of the Organization Committee.

Two objectives of the Congress as outlined by the Secretariat are: (1) to consider the question of the stability and stabilization of medicaments from different points of view; and (2) to give the opportunity to the scientists in the whole field of pharmacy to report on their scientific work.

Accordingly, "Stability and Stabilization of Remedies," will be the principal subject covered at the Congress with five international specialists in the field participating in a symposium. In addition, reports under the following subjects will be covered:

1. Pharmacognosy and cultivation of drugs.
2. Pharmaceutical chemistry and biochemistry.
3. Galenical pharmacy.
4. Biology and pharmacology.

The tentative program for the Congress is as follows:

Sunday, September 6

5:00 P.M. Session of the Council of the Scientific Section and of the Organization Committee.

8:30 P.M. Assembly and welcome of the participants.

Monday, September 7

9:30 A.M. Opening of the Congress.

Welcome by a representative of the Swiss authorities.

Introduction by the President of the Scientific Section, Prof. Dr. R. Ruyssen.

Greetings by the President of the International Pharmaceutical Federation, Sir Hugh Linstead.

10:00 A.M. Symposium: Stability and Stabilization of Medicaments—

Stability of Medicaments—general introduction, problems, methods of testing the stability, etc.—Prof. Dr. S. A. Schou, Copenhagen.

Decomposition of Medicaments Due to Physical Changes—Prof. Dr. Guillot, Paris, France.

Decomposition of Medicaments Due to Chemical Changes—Prof. Dr. E. H. Vogelenzang, Leyden, Belgium.

3:00 P.M. Communications in the Different Sections:

1. Pharmacognosy and Cultivation of Drugs.
2. Pharmaceutical Chemistry and Biochemistry.
3. Galenical Pharmacy.
4. Biology and Pharmacology.

Tuesday, September 8

9:00 A.M. Symposium: Stability and Stabilization of Medicaments (cont)

Decomposition of Medicaments Due to the Action of Bacteria and Fungi—Dr. Fust, Basle, Switzerland.

10:30 A.M. Communications in the Different Sections.

3:00 P.M. Communications in the Different Sections.

6:30 P.M. Tour of the Lake of Zurich by boat (dinner at Rapperswil).

Wednesday, September 9

9:00 A.M. Symposium: Stability and Stabilization of Medicaments (cont)

Decomposition of Medicaments Due to Auxiliary Substances and Containers of Remedies —M.T.D. Whittet, London, England.

10:30 A.M. Communications in the Different Sections.

3:00 P.M. Communications in the Different Sections.

Thursday, September 10

9:00 A.M. Discussion of the papers of the Symposium.

10:30 A.M. Final Session of the Congress.

11:30 A.M. Departure for the pharmaco-botanical excursion.

Friday, September 11

Visit to the pharmaceutical industries in Basle and Berne.

The authors of the scientific papers and all other participants are asked to send their registration to the secretariat of the Congress before June 15. The address is: Prof. Dr. K. Steiger-Trippi, Pharmaceutical Institute of Technology, Clausiusstrasse 25, Zurich, Switzerland.

Also, authors of scientific papers are asked to send the title and resume of their reports (one page typewritten) in duplicate, to the secretariat of the Congress not later than June 15.

WHO Recommends International Non-Proprietary Names

The World Health Organization has transmitted to the United States Public Health Service a list of names which WHO has selected as recommended international non-proprietary names for pharmaceutical preparations. This list, appearing below, includes names which are recommended in accordance with procedures adopted in 1955 and the procedure for the selection of these names, including earlier publication and review as proposed names, has been completed. WHO is now requesting that these recommended names be recognized as the non-proprietary names for the substances concerned, and that countries take the necessary steps to prevent the acquisition of proprietary rights in the names.

This list will be published in a forth-coming issue of the *Chronicle of the World Health Organization.* This is the second list of recommended names to be released by WHO. The first list was published in the June, 1955, issue of the *Chronicle,* (Vol. 9, No. 6).

RECOMMENDED INTERNATIONAL NON-PROPRIETARY NAME	CHEMICAL NAME OR DESCRIPTION
acetylmethadol	6-dimethylamino-4,4-diphenyl-3-acetoxyheptane
alphacetylmethadol	α-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane
alphamethadol	α-6-dimethylamino-4,4-diphenyl-3-heptanol
anileridine	1-[2-(p-aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester
betacetylmethadol	β-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane
betamethadol	β-6-dimethylamino-4,4-diphenyl-3-heptanol
betaprodine	β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine
desomorphine	dihydrodesoxymorphine
diethylthiambutene	3-diethylamino-1,1-di-(2-thienyl)-1-butene
dimethylthiambutene	3-dimethylamino-1,1-di-(2-thienyl)-1-butene
dipipanone	4-4-diphenyl-6-piperidino-3-heptanone
ethoheptazine	1-methyl-4-carbethoxy-4-phenylhexamethyleneimine
ethylmethylthiambutene	3-ethylmethylamino-1,1-di-(2-thienyl)-1-butene
hydroxypethidine	1-methyl-4-(3-hydroxyphenyl)-piperidine-4-carboxylic acid ethyl ester
levallorphan	*l*-3-hydroxy-N-allylmorphinan
levorphanol	*l*-3-hydroxy-N-methylmorphinan
metethoheptazine	1,3-dimethyl-4-carbethoxy-4-phenylhexamethyleneimine
metheptazine	1,2-dimethyl-4-carbomethoxy-4-phenylhexamethyleneimine
methyldesorphine	6-methyl-Δ^6-desoxymorphine
methyldihydromorphine	6-methyldihydromorphine
myrophine	myristyl ester of benzylmorphine
normethadone	4-4-diphenyl-6-dimethylamino-3-hexanone
oxpheneridine	1-(2-phenyl-2-hydroxyethyl)-4-carbethoxy-4-phenyl-piperidine
oxymorphone	dihydrohydroxymorphinone
phenomorphan	3-hydroxy-*N*-phenethylmorphinan
proheptazine	1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine
properidinum	1-methyl-4-phenylpiperidine-4-carboxylic acid isopropyl ester
propoxyphene	4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane

► *Rho Chi Society,* national pharmacy honorary society, has recently elected new officers who will be installed at the close of the 1959 Convention to serve for a two year term. Dr. Louis W. Busse, Associate Dean, School of Pharmacy, University of Wisconsin, was elected national Vice-President and Dr. Edward J. Rowe, Professor of Pharmacy, College of Pharmacy, Butler University, was elected national Secretary-Treasurer.

AMERICAN HOSPITAL FORMULARY SERVICE

► THE AMERICAN HOSPITAL FORMULARY SERVICE has been accepted with considerable enthusiasm and the first printing is nearly depleted. A second printing is underway and additional copies will be available July 1, 1959. Orders may be directed to The Hamilton Press, Hamilton, Illinois. The price of single copies, including supplements for one year, is $15.00.

The SOCIETY's Committee on Pharmacy and Pharmaceuticals, working under the direction of Dr. William Heller, is preparing monographs to be included in the Supplements. It is anticipated that the First Supplement to the Formulary Service will be available within the next few months.

Subscribers will want to note that extra copies of the binder are available from The Hamilton Press at $4.00 each. Some individuals using the entire set of monographs have suggested that a second binder is helpful. Also, blank pages, for use in the Formulary Service in connection with preparing monographs not available, may be ordered from The Hamilton Press. One ream (500 sheets) is available for $3.00; two reams (1,000 sheets) cost $5.40.

Since this is a continuing service, classifications have been included for which there are presently no monographs. It is anticipated that these will be made available in future supplements.

Suggestions or questions with regard to monographs or contents of the Formulary Service may be directed to Dr. William Heller, Chairman, Committee on Pharmacy and Pharmaceuticals, Pharmacy Department, University of Arkansas Medical Center, Little Rock, Arkansas.

★ TEXAS SEMINAR

by ADELA SCHNEIDER

► NINETY-SEVEN REGISTRANTS for the Eleventh Annual Seminar for Hospital Pharmacists, held at the University of Texas College of Pharmacy, February 14-15, heard an outstanding faculty present papers of timely interest.

The program opened on Saturday morning with Cedric Jeffers, Scott and White Hospitals, Temple, presiding. The invocation was by Dr. Edward Heinsohn of the University Methodist Church in Austin, after which greetings were extended by Dean Henry W. Burlage of the College of Pharmacy and by James D. McKinley, Jr., of Houston, President of the Texas Society of Hospital Pharmacists.

Dr. Harold Dobson of the Department of Medicine, Baylor University, Houston, presented the opening address which was a description of the operations of the Gulf Coast Poison Information Center located in Houston. Dr. Dobson made suggestions to the hospital pharmacists who might be called on at some time to help establish such centers in either small or large cities, emphasizing that one of the greatest problems is finding the finances with which to operate.

After a break for coffee, Robert Bogash, President of the ASHP, brought greetings from the Executive Committee and gave a talk entitled "Potpourri in Three Parts," in which he discussed some "un-looked-for" circumstances that sometimes occur in hospital pharmacy. In a more serious vein, he challenged the group to familiarize themselves with some of the new equipment now made available to hospital pharmacists for use to great advantage, as in the field of prepackaging.

The afternoon session, conducted by Alice Green, of Robert B. Green Hospital, San Antonio, consisted of panel discussions and Clinic sessions.

The first panel was on the Pharmacy and Therapeutics Committee in Hospitals with special emphasis on organization of the Committee and number of meetings necessary for effective functioning. The value of the Committee in proper functioning of the formulary in a hospital was also stressed by Leo Godley, Harris Hospital, Fort Worth, who moderated the panel, and by the panel members Cedric Jeffers; Lewis Smith, Baylor Hospital, Dallas; Robert Lantos, University of Texas Medical Branch in Galveston, and Louise Pope, University of Arkansas, Little Rock.

The next panel was on the use of the American Hospital Formulary Service and was of particular interest to the hospital pharmacists who had just a day or two previously received their copies of the Formulary and to those expecting them. Guy Kelly, Methodist, Hospital, Dallas, moderated the panel, with Cedric Jeffers, Lewis Smith, and George Provost of the University of Arkansas, as members. Mr. Provost's comments were especially of interest since he had worked with Dr. William Heller in the compilation of the Formulary.

The registrants then broke up into groups for the clinic sessions to discuss the following subjects: The Use of Disposables, The Role of a Detail Man in the Hospital Pharmacy, Pharmaceutical Problems in Small Hospitals and Pricing.

The Sunday morning session opened at 9:30 following the second session of the annual meeting of the Texas Society of Hospital Pharmacists. William F. Clarke, Jr., V.A. Hospital, Waco, was chairman of the session which featured first an evaluation of the first year's operation of the Gulf Coast Poison Information Center in Houston by Ruth Kroeger of the School of Pharmacy, Texas Southern University, Houston.

Dr. A. B. Cairns, Pathologist at Methodist Hospital, Dallas, then presented a timely discussion of the current status of hospital disinfectants which proved of major interest in our day of high incidence of staphylococcus infections.

The final paper of the morning was a Report on the Audit of Pharmaceutical Service in Hospitals by Clifton J. Latiolais who was assistant director of the Audit, and is now Director of Pharmacy Service at the Health Center at Ohio State University.

A panel on "What Is Your Problem?" was moderated by Leo Godley in which the experts—Clifton Latiolais, Dr. Cairns, Dr. Hobson, and Robert Bogash—were called on to answer questions covering the subjects they had discussed.

The afternoon session was presided over by Adela Schneider, Southern Pacific Hospital, Houston, who introduced the only speaker of the afternoon, Dr. Charles O. Wilson of the University of Texas College of Pharmacy. His paper, titled "Pharmaceutical Jungle," was a treatise on generic name selections and the chemical nomenclature in which, as in a jungle, pharmacists can easily become confused and possibly even lost.

Miss Schneider then presented Dean Burlage who took charge of the rewarding part of the program—the awarding of certificates to the registrants.

Besides the ninety-seven who registered and the faculty of the Seminar, there were in attendance at several of the sessions members of the College of Pharmacy of the University of Texas. Among the registrants was William E. Woods of the National Pharmaceutical Council, New York City, who had been director of the Sixth and the Seventh Annual Seminars at the University.

Installation of officers of the Texas Society. Shown left to right are Robert Bogash, ASHP President, who did the installing; and new officers Guy Kelly, President; Blanche Groos, Treasurer; and Paul Wilburn, Vice-President, The Secretary, Alice Green, was not present

Group photo showing enrollees at 1959 Texas Seminar

SELECTED PHARMACEUTICAL ABSTRACTS

and summaries of other articles interesting to hospital pharmacists

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edited by CLIFTON J. LATIOLAIS, HENRY J. DEREWICZ *and* LEO F. GODLEY

DRUG RESIDUES IN FOOD ANIMALS

Drug Residues in Food Animals, Lehman, A. J., Bull. Parenteral Drug Assoc. 12:24 (Nov.-Dec.) 1958.

Concern is directed to the problem of tissue residues of food animals from veterinary drugs. The FDA is presently authorized to establish tolerance limits for a wide varity of chemicals. Before any poisonous or deleterious substances is permitted for use on farm animals, it must be demonstrated that: (1) the evidence is adequate to show no residue in the edible parts, or (2) if a residue is present it must be shown that the residue is completely described before the food is eaten, or (3) if a residue is present in the food as it is eaten, evidence must be shown that the food is safe. To fulfill the three requirements, the following information must be obtained: (1) toxicity of the substance employed, (2) an analytical method of sufficient sensitivity for detecting the residue or demonstrating its absence, and (3) competent studies to show either no residue, or what residue is present in all food items from treated animals. The method of obtaining the needed information is outlined in detail.

NORMAN HO

STABILITY OF VITAMIN A

Durability of Vitamin A in Some Oils, Maciag, I., Acta Poloniae Pharmaceutica 15:447, 1958.

The author has examined the behavior of Vitamin A in some crude and refined oils, namely in rape-seed, arachid and soja oils.

The results disclose that the rate of decomposition of Vitamin A in oily solutions, preserved in daylight conditions, depends upon the intensity of exposition to light. Moreover she ascertained that the content of hyperoxides in the oils, as determined in her experiments, does not play the decisive role in the rate of decomposition of Vitamin A.

Finally, the author established the fact that of the three examined kinds of oil, soja oil contains the most durable solutions of Vitamin A.

AUTHOR'S ABSTRACT

CARBOPOL AS SUSPENDING AGENT

Pharmaceutical Applications of the Sodium Salt of Carbopol 934, Lee, J. A. and Nobles, W. L., J. Am. Pharm. Assoc., Sci. Ed. 48:92 (Feb.) 1959. (University of Mississippi College of Pharmacy; a product of B. F. Goodrich Chemical Company.)

A study was undertaken in an effort to evaluate the suspending and emulsifying properties of the dry sodium salt of Carbopol 934. Carbopol 934 is a hydrophilic colloid originally designed as a thickening agent for various types of aqueous formulations. It is a high molecular weight polymer containing a large percentage of carboxyl groups. Essentially, it is a carboxylic vinyl polymer supplied as a finely divided white powder. It disperses readily in water to yield an acid solution of low viscosity.

Carbopol salts were found to be excellent suspending agents for calamine, neocalamine, zinc oxide and a kaolin-pectin combination to mention a few. This product has also found commercial application as an emulsion stabilizer and/or a primary emulsifier. Satisfactory emulsification was obtained using liquid petrolatum, cod liver oil and cottonseed oil.

This study indicates that a number of medicinal agents can be satisfactorily suspended or emulsified using Carbopol 934. In general, 0.5% of the dry sodium salt appears to be the optimum concentration for suspending purposes.

THOMAS E. ARKINSON

STERILIZATION OF LIQUIDS

Factors Influencing the Course of Sterilization of Liquids by Heating when a Bactericidal Substance is Present, Zathurecky L. and Mariasova E., Farmacia (Czechoslovakia) 27:330 (Nov.) 1958.

In order to clarify the influence of various conditions upon the sterilization of the 5% solution of glucose by means of heating when 0.001% phenylmercuric borate is present, the authors have undertaken a study with the following results: (1) the time which is necessary for the temperature to reach 100°C. is to be added to the time of heating required for sterilization; (2) the temperature of the solution is to be held at 98° - 100°C. during 30 minutes in any case when an absolutely sterile product is to be obtained; even a period of 27 minutes was found insufficient; (3) by increasing the interface between heated air and the solution to be sterilized, i.e. by using more flasks with smaller content, it is possible to reduce the time needed for sterilization; and (4) the quality and thickness of glass of the flasks used exert little influence upon the course of sterilization.

HUBERT ZACEK

GLYCERYL TRINITRATE, DETERMINATION OF

Determination of Glyceryl Trinitrate by Nitrite Method, Hansen, G., Arch. Pharm. Chem. 65:541, 1958.

Nitrite is produced when glyceryl trinitrate is decomposed with sodium hydroxide, the quantity obtained being constant even when experimental conditions are varied. Heating 25 ml. of glyceryl trinitrate solution (10 percent) with 3 ml. of 2N sodium hydroxide in a water bath for 10 minutes, or allowing to stand at room temperature for 1 hour, yields nitrite equivalent to 63.2 percent of the nitrogen present. The quantity of nitrite in the reaction mixture may be determined by diluting and adding a reagent consisting of ethyl-*alpha*-naphthylamine hydrobromide 8 mg., procaine hydrochloride 250 mg., 2N acetic acid 100 ml. The solution is allowed to stand for 30 minutes, and the light absorption measured at 525 mu. The color intensity is proportional to the quantity of nitrite in the sample. A correction is made for the nitrite content of the sample, determined separately. This method is stated to be sensitive, reproducible, and specific for alkyl nitrates. Some excipients, such as agar, interfere in the determination, and the alkaline solution must not be heated if lactose is present.

AUTHOR'S SUMMARY

DISTINGUISHING QUININE FROM QUINIDINE

Rapid Chemical Method for Distinguishing Quinine from Quinidine, Petkovic, M., Acta Pharm. Jug. 8:7, 1958.

About 10 mg. of base or salt is placed in a watchglass, and about 1 ml. of ethanol (96 percent) added. After the solid has dissolved, one drop of dilute sulfuric

acid is added and mixed thoroughly with the solution. A drop of solution is placed on filter paper and treated with iodine vapor for 30 seconds. Spots due to quinine appear grey-blue to grey-purple with a dark yellow edge, and those due to quinidine dark yellow, changing to yellow on allowing to stand in the air.

AUTHOR'S SUMMARY

GASTRIC MUCOUS, EFFECT ON TABLET DISINTEGRATION

A Preliminary Report of the Effect of Gastric Mucous upon Tablet Disintegration, Abbott, D.D., Packman, E.W., Rees, E. W., Harrison, J.W.E., J. Am. Pharm. Assoc. Sci. Ed., 48:19 (Jan.) 1959. (Harrison Research Laboratories).

Preliminary investigation into the effect on tablet disintegration was initiated from the observation that various aspirin-containing preparations showed varied absorption patterns while at the same time exhibiting comparable *in vitro* disintegration times.

Other studies have shown that aspirin is absorbed from the stomach. Using this as a premise, it was surmised that the relative presence of mucoid material would affect the absorption rate. Accordingly, an *in vitro* study was developed using simulated gastric juice, U.S.P., and two samples of pooled human gastric juice, each containing a different amount of mucoid substance that is normally present in gastric juice. In addition, a sample of mucoid substance was used to determine what could conceivably occur if a tablet were ingested on a fasting stomach or without water. The method used for determination was the basket-rack apparatus and procedure described in U.S.P. XV. Seven varieties of tablets were used, and each subjected to the four test samples.

Gastric mucoid substance has a pronounced effect on prolonging the *in vitro* disintegration time of the tablets tested. The *in vitro* disintegration time in pooled human gastric juice is greater than that of simulated gastric juice, and *in vitro* disintegration is prolonged in simulated gastric juice if the tablets are first exposed to mucoidal substance from human gastric juice.

J. A. OLIVER

REINFORCEMENT OF ACTION OF ALKALOIDAL EYE-DROPS

Reinforcement of the Action of Alkaloidal Eye-Drops by Previous Instillation of Sodium Borate Solution into the Eyes, Hammarlund, E. R.; Boberg-Ans, J.; and Grove-Rasmussen, K. V., Dansk Tidsskrift for Farmaci 33:10 (Jan.) 1959. (Royal Danish School of Pharmacy, Department of Pharmacy, Copenhagen, the Finsen Institute, Eye Department, Copenhagen, and the Finsen Institute and the Radio Centre, Pharmaceutical Department, Copenhagen.)

Since the physiological effect of alkaloidal eye-drops results from an absorption of the free base portion of the alkaloid, greater response could be obtained if the drugs were administrated in alkaline form. However, because of the resulting unstability of the alkaloids, it is not conveniently possible. This paper describes a technique whereby one may obtain the normal physiological response from a much less than normal concentration of alkaloidal eye-drops by means of the previous instillation to the eyes of one drop of isotonic sodium borate solution, 2.6 percent and pH 9.2. The sodium borate solution momentarily buffers the eye to a sufficient degree of alkalinity to allow a greater absorption of the various alkaloidal eye-drops. Experimental and clinical investigations support the efficiency of the technique. There is no discomfort to the patient from the use of alkaloidal eye-drops in this manner. Further experimental and clinical investigations are in progress and will be reported later.

AUTHOR'S SUMMARY

PHENOBARBITAL DETERMINATION

Nephelometric Determination of Phenobarbitone (5-Ethyl-5-Phenylbarbituric Acid), Kalinowski, K. and Baran, H., Acta Poloniae Pharmaceutica 15:327, 1958.

The authors have described their nephelometric method of determining phenobarbitone; for this purpose they applied the reaction of Luminal with mercury perchlorate, using a Pulfrich nephelometer.

They carried out the determination of the relative and absolute turbidity of Luminal solutions; then they presented by curves the relation of relative and absolute turbidity of phenobarbitone to its concentration.

This method makes it possible to determine Luminal within the limits of 0.000100 to 0.000350 Gm. The error of this method does not exceed $\pm$ 4%. Using the described procedure the analysis may be perfomed within about 5 minutes.

AUTHOR'S ABSTRACT

THIAMINE ASSAY IN THE PRESENCE OF INTERFERING SUBSTANCES

The Gravimetric Silicotungstate Method of Assay for Thiamin in the Presence of Interfering Substances, Vannatta, E. E. and Harris, L. E., J. Am. Pharm. Assoc., Sci. Ed. 48:34 (Jan.) 1959. (College of Pharmacy, Ohio State University, Columbus, Ohio.)

The gravimetric method of essay of thiamin is used after a preliminary separation of the thiamin from such interfering substances as may be found in B-complex elixirs, multiple vitamin capsules containing trace minerals, B-complex tablets and capsules with iron among others. The separation is accomplished by adsorption of thiamin on columns of Amberlite IRC-50 (a weakly acidic, carboxylic, cation-exchange resin). Following ellution of the thiamin, a quantitative determination of thiamin is accomplished using the gravimetric method of assay described by the author.

HENRY J. DEREWICZ

ODORS

Olfaction—A Comparison of Homogeneous and Heterogeneous Adaptation, Moncrieff, R. W., Manufacturing Chemist 30:22 (Jan.) 1959.

Smelling one odorant can reduce the sensitivity of the nose for another odorant smelled immediately afterwards. This so-called olfactory adaptation has been used to classify odors. Experimental studies were made of adaptation in two homogeneous pairs:

(1) acetone as the adapting odorant followed by acetone as the test odorant (self-adaptation),
(2) isopropanol as the adapting odorant followed by isopropanol as the test odorant (self-adaptation);

and in two heterogeneous pairs:

(1) acetone as the adapting odorant, followed by isopropanol as the test odorant (cross-adaptation),
(2) isopropanol as the adapting odorant, followed by acetone as the test odorant (cross-adaptation).

A range of concentrations of odorant was offered to the observer in random order, together with interspersed reliability checks of bottles containing diluent only and no odorant. Precautions were taken to secure objectivity and reproducibility of response.

The results of the experiment showed that in so far as acetone and isopropanol were concerned, homogeneous adaptation is very much greater than heterogeneous adaptation. The implication is that the pathway from the receptor to cortex that is traversed when acetone is smelled is only slightly distrubed by even intense activation of that pathway followed when isopropanol is smelled, and vice versa. Yet the acetone pathway is itself very greatly disturbed, one sniff of pure acetone raising the threshold concentration for the next sniff by 170 times.

ROBERT L. RAVIN

PSYCHOLOGY OF CLINICAL TRIALS

The Psychology of Clinical Trials, Kennedy, A., Pharm. J., 182:5 London (Jan. 3) 1959.

The author goes to some length in discussing the psychology of the practical and statistical aspects of therapeutic trials. Both the aims and techniques employed in clinical experimentations are discussed with particular reference to the use and abuse of statistics, observer and subject errors, and the hypothesis and design of such trials.

From the evidence presented, the author concludes that: (1) the human error, present in every clinical trial, must be minimized by statistical and clerical methods, (2) the accurate testing of a drug requires time and no ingenuity in planning can reduce this below a certain minimum, (3) all results, negative, positive

and apparently irrelevant, must be recorded, and (4) the most serious errors are usually committed during the early stages of planning.

Suggestions are presented in an effort to improve the integrity of future therapeutic trials. Closer examination of the time and sequence of dosage, the extent of trials on normal volunteers, the coordination between the manufacturer, physician and statistician, and the training of the researchers will help avoid many present day difficulties.

ROBERT W. MAHONEY

VITAMIN D DETERMINATION IN THE PRESENCE OF VITAMIN A

A Photometric Determination of Vitamin D in Presence of Vitamin A, Schmall, M.; Senkowski, B.; Colarusso, R.; Wollish, E.; and Shafer, E., J. Am. Pharm. Assoc., Sci. Ed. 47:839 (Dec.) 1958. (Analytical Research Laboratory, Hoffmann-La Roche, Inc., Nutley, N. J.)

A procedure suitable for the relatively rapid photometric determination of vitamin D in presence of vitamin A in simple mixtures, such as dry vitamin A and D powders and some multivitamin preparations, is presented as a "Basic Method," using chromatography on Florex XXS. Modifications of the method to provide application of the procedure to numerous polyvitamin products also are described. The great diversity of formulations of such preparations may necessitate the use of various techniques for the removal of interfering substances. Several of these techniques, such as preliminary extraction with petroleum ether or the use of an alumina or polyethylene powder chromatographic column in conjunction with the "Basic Method," are provided. The advantages and limitations of the different modifications are discussed. A comparison of results with those obtained by the U.S.P. bioassay procedure shows the accuracy and precision obtainable.

AUTHOR'S SUMMARY

DIELECTRIC CONSTANTS IN SOLVENT SYSTEM BLENDING

The Use of an Approximate Dielectric Constant to Blend Solvent Systems, Moore, W. E., J. Am. Pharm. Assoc., Sci. Ed. 47:855 (Dec.) 1958. (Sterling Winthrop Research Institute, Rensselaer, N. Y.)

The author discusses a technique which may be used to blend solvents by manipulating dielectric constants. Briefly, the method consists of first determining a suitable solvent which is adequate for the concentration of solute desired. Next, the dielectric constant for this solvent must be determined. Finally, a varied number of solvents is chosen which are miscible or soluble in themselves and by using the alligation method, percentages of the solvents are determined which will produce the desired approximate dielectric constant. The author also presents tables indicating various mixtures or blends of solvents and their dielectric constants which were used to solubilize various substances such as barbiturates, hormones and steroids.

HENRY J. DEREWICZ

DEXTRAN INJECTIONS

A Note on Particulate Matter Encountered in Some Dextran Injections, Cadwallader, D. E., Jr.; Becker, C. H.; Winters, J. H.; and Marcus, D., J. Am. Pharm. Assoc., Sci. Ed. 47:894 (Dec.) 1958. (University of Florida College of Pharmacy, Gainesville, Fla.)

Dextran injection is an important blood volume expander. In case of a national emergency, possible large scale usage dictates that military depots must stock pile dextran injection in large quantities. As a consequence, this preparation is stored over a long period of time. During this storage period, however, a precipitate has been observed to form, thereby rendering the preparation unfit for intravenous injection.

The preparation is a colloidal infusion, available commercially as a six percent solution of partially hydrolyzed dextran in isotonic sodium chloride solution. Solutions which contained particulate matter were manufactured by three different companies. All varied in date of manufacture, lot number and conditions under which they were stored. Yet all carried a precipitate averaging approximately 1 mg. per 500 ml flask.

Experimental procedure revealed the following: The precipitate was found to be primarily flocculent and did not conform to any apparent pattern of size, shape, or color. The precipitate was found to be very closely related to dextran, i.e., a dextrose polymer which must aggregate in some manner to form a "snowflake" particle and settle out of solution.

A satisfactory procedure for solubilizing the particles in dextran injection is to autoclave the solution for thirty minutes at 15 pounds pressure and 121°. This re-dissolving of the particles is apparently irreversible, since there is no re-precipitation on cooling, freezing, or concentrating the solution.

THOMAS E. ARKINSON

ABSORPTION OF ANALGESIC TABLETS

Comparative Rate of Absorption of Four Commercial Analgesic Tablets, Harrisson, J. W. E., Packman, E. W. and Abbott, D. D., J. Am. Pharm. Assoc., Sci. Ed. 48:50 (Jan.) 1959. (La Wall and Harrisson Research Laboratories, Philadelphia, Pa.)

By measuring the plasma salicylate or blood *p*-aminophenol levels of fifteen male subjects between the ages of twenty-one and thirty-five, the authors concluded that the degree of absorption at various time intervals of acetylsalicylic acid and acetophenetidin following the administration of tablets containing these substances varies within the individual subject from day to day as widely as it does between different subjects. The variation in response between tablets can be influenced by differences in their physical properties or composition, but it is also probable that the great differences which do occur may be due to the widely varing physiologic state of the subject. It was possible to demonstrate salicylate in the plasma within one to two minutes after ingestion of tablets containing aspirin at a dose level of seven to ten grains and *p*-aminophenol was present in the blood of about fifty percent of the subjects within eight minutes.

A. GORDON MOORE

CURRENT LITERATURE

. . . also calling your attention to the following articles appearing in recent hospital and pharmaceutical journals

. . . . . .

ADMINISTRATION

—General

Swanson, A. L.: What the Administrator Expects from the Pharmacist, *Hosp. Pharmacist* (Canada) 12:15 (Jan.-Feb.) 1959.

—Control

McCluskey, Clay M.: Drug and Solution Control (Part III), *Hosp. Management* 87:100 (Apr.) 1959.

—Dispensing

Croumey, Edward F.: How To Make After-Hours Dispensing Safe, *Modern Hosp.* 92:118 (Mar.) 1959.

—Inventory

Mayne, Kenneth R.: Hospital Pharmacy Inventory Control, *Am. Profess. Pharm.* 25:115 (Feb.) 1959.

—Policies

Sperandio, G. J.: The Pharmacy Department's Statement of Policies, *Tile and Till* 45:27 (Mar.-Apr.) 1959.

EDUCATION

Bartilucci, A. J.: The Five-Year Program in Pharmacy, *Hosp. Progress* 40:112 (Mar.) 1959.

FORMULARY SERVICE

Parker, Paul F.: The American Hospital Formulary Service, *J. Am. Assoc., Pract. Pharm. Ed.* 20:154 (Mar.) 1959.

RADIOISOTOPES

Satterfield, Robert W.: Caution Signs for Radioisotope Handling, *Hospitals, J. A. H. A.* 33:75 (Mar. 16) 1959.

RESEARCH

Stauffer, Isabel E.: Research in Hospital Pharmacy, *Hosp. Pharm.* (Canada) 12:17 (Jan.-Feb.) 1959.

DRUG EVALUATIONS

by the Council on Drugs of the American Medical Association

► THE FOLLOWING MONOGRAPHS and supplemental statements on drugs have been authorized by the Council on Drugs of the American Medical Association for publication and inclusion in *New and Nonofficial Drugs*. They are based upon the evaluation of available scientific data and reports of investigations. In order to make the material even more valuable, dosage forms and preparations of individual drugs have been added to the monographs. These dosage forms and preparations were not taken from material published in the *Journal of the American Medical Association* by the Council on Drugs; rather, they were obtained from such manufacturers' brochures, news releases, etc., which were available to us at the time of publication. An attempt has been made to make the list of dosage forms as complete as possible. However, no guarantee can be made that the list of preparations is complete and it is suggested that hospital pharmacists consult manufacturers' releases for additional dosage forms and preparations.

The issues of the *Journal of the American Medical Association* from which each monograph has been taken is noted under each monograph. Monographs in this issue of the JOURNAL include those published in the *Journal* Jan. 31 1959.

Notice

New and Nonofficial Drugs 1959 is now available from your local bookstore and from the publishers, J. B. Lippincott Company, Philadelphia, Pa. This 1959 edition contains monographs of drugs evaluated by the Council on Drugs of the American Medical Association and published in the Journal of the A.M.A. to January 1, 1959. The index listed below contains those drugs evaluated and published between December 20, 1958 and January 31, 1959.

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TO ARTICLES IN THIS ISSUE

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TO EVALUATED DRUGS IN THE FEBRUARY AND MARCH 1959 ISSUES OF THE AMERICAN JOURNAL OF HOSPITAL PHARMACY

Report to the Council

The Council has authorized publication of the following report.
H. D. KAUTZ, M.D., *Secretary.*

The following report has been adopted by the Committee on Research.
NORMAN DE NOSAQUO, M.D., *Secretary.*

EXPERIMENTATION IN MAN

HENRY K. BEECHER, M.D., BOSTON

Present Aims

► EXPERIMENTATION IN MAN for scientific purposes is as old as recorded history. The need for constant examination of the procedure is equally ancient. This is required by progress in science and by the advance of ethical and moral concepts.

In the two decades just passed, two reasons have emerged which especially point up the need for a new review of the subject. First, there were the outrages of Hitler's Germany. The puzzle is how such things could have occurred in modern society. Although the philosophical problems raised by those gross actions are beyond the area surveyed in this report, they too indicate the need for a long, straight look at our current practices. Second, there is the rather newly recognized fact that some types of basic scientific advance can be made only in the presence of disease. Nature presents us with bolder experiments than

From the Anesthesia Laboratory, Harvard Medical School at the Massachusetts General Hospital.

we would ever dare to perform ourselves. We profit from a study of them—basic science profits. Having seen what fundamental ends can be achieved, the experimentalist is led to carry on where Nature leaves off. The purposes of human experimentation thus become deeper and more complex than ever before, and so also do the problems surrounding it, reasons enough for this study.

In most cases, the problems of human experimentation do not lend themselves to a series of rigid rules. Although one purpose of the present study is to set down views, concepts, and even "rules" that have been accepted by one group or another, this is done so that the investigator, troubled by a given problem, can find references to past thinking on this subject, and so that he can have a framework against which he can measure his problems in terms of the experiences and conclusions of others in similar situations. The breaches of ethical conduct which have come to my attention were owing to ignorance or thoughtlessness. They were not willful or unscrupulous in origin. It is hoped that the material included here will help investigators protect themselves from the errors of inexperience.

Finally, it can be said that, while human experimentation has accompanied the practice of medicine from times of antiquity, the current concept of medical research has not really been presented as such to the courts. As the courts have understood it, human experimentation has not been, nor is it now, legally recognized as a legitimate part of the physician's activities. "So far, planned and directed medical research on human beings has not been tested."[1] The universal and long-standing recognition that research is essential to the advancement of medical science and the newer recognition that some aspects of basic science cannot advance without it have led to a correct, although still extralegal, expansion of human experimentation. Curiously, such work, when well conceived and soundly conducted, is everywhere recognized as being properly within the ethical and moral concepts of our time; yet it remains outside legally. Legal inclusion will depend on an understanding of all the facets of the problem.

Brief History

The oldest world literatures contain references to experimental work with animals and man.[2] It was the practice in ancient Persia for the king to hand over condemned criminals for experimental purposes in science. Later the Ptolemies did the same in Egypt.[3] About 1,800 years ago Galen, the founder of experimental physiology,[4] somewhat formalized medical experimentation, but this fell under a cloud during the Dark and Middle Ages, until Vesalius in the 16th century overrode the proscription against dissection of the human body and demonstrated certain errors in Galen's concept of the circulation of the blood. Three generations later Harvey, after carrying out controlled experiments in animals and in man,[2] demonstrated the circulation of the blood. He showed, in particular, that all the blood had to pass through the heart (if his calculations of volume and velocity were correct), and thus the first idea of measurement in biological investigation bore fruit.[4] More than 100 years later, Lind, in 1747, carried out a remarkably well-controlled study and demonstrated that oranges and lemons could cure scurvy. A half-century after this, in 1798, Jenner, after controlled experiments in man, published his proof of the value of vaccination against smallpox. The world was ready for two of its greatest experimentalists, Claude Bernard and Louis Pasteur.

However, all was not smooth sailing for the eager investigator. Experimentation on other men requires a willingness to experiment upon oneself as evidence of good faith, although in a given case self-experimentation may be wholly impractical. When it is carried out, it must be done with the same safeguards that are applied to other subjects. Ivy[2] cites a number of examples to indicate that willingness without the discipline of proper controls can be misleading or devastating, or both, to the participant. In 1767, John Hunter inoculated himself with gonorrheal pus to prove that the disease was transmissible in this way. He succeeded. But from the same inoculum he also acquired syphilis and concluded that gonorrhea and syphilis were merely manifestations of the same disease. Purkinje gave himself enough digitalis to kill nine cats, so that he might study the visual changes in himself. He had cardiac pain and irregularity and vomited for a week. Hales, enthusiastic about the marvels of intravenous injection, received a half-ounce of castor oil by this route and lived to describe its remarkable effects. In 1830, Tonery, in order to convince the French Academy of the extraordinary powers of charcoal to absorb alkaloids, took with this safeguard a dose of strychnine which, without it, would have been lethal. In 1857, carbon tetrachloride was tried as an anesthetic in man; a few animal experiments would have shown it to be unsuitable. In 1894, Oliver told Schafer that he had made extracts of all the endocrine glands and had injected them into his own son. Schafer altered the experiment and was first to demonstrate the pressor effect of epinephrine in dogs and cats. Ivy concludes that "these experiments may be a tribute to the enthusiasm and bravery of these early medical scientists, but they clearly show the limitations and dangers of uncontrolled self-experimentation."

At the present time we find that able men are still in difficulties. When one shifts from a study of objective manifestation of disease to subjective effects, specifically, for example, to a quantitative study of the effects of drugs on symptoms, it becomes apparent that added controls are mandatory. Chief among these is the use of the double-unknowns approach to eliminate bias. This procedure is not possible when the experimenters are also the subjects, who, as drug experience and sophistication grows, cannot remain in ignorance of the "aura" produced by opiates, for example. The scores of studies that have been lost because of a failure to recognize and employ adequate controls have been reviewed elsewhere.[5]

Paradoxically enough, in the last century at least, those who experiment in man have been freer of attack than those who carry out animal experimentation. The ethics of human experimentation will be discussed later.

Scope

There are many good reasons for a careful consideration of the scope of human experimentation: protection of the subjects, the goals of the investigators, their research and their institutions, and the sound development of medicine. These all require a levelheaded approach to experimentation in man.

Comparatively recent developments in medicine and changes in emphasis give added weight to an examination of human experimentation at this time. Although prior experimentation in animals is absolutely necessary when possible, the crucial study of new techniques and agents must be carried out in man. The extraordinary skill of the organic chemist and the biologist, working together in identifying active agents in natural products, and the chemist's progress in creating new and promising compounds, which ultimately must be tried out in man, throw an exceptionally heavy load on the experimentalist. Man as the final test site has come into prominence only in recent decades. The current development of human biochemistry, human physiology, and human pharmacology has made it plain that man is the "animal of necessity" here. In addition, there is a new interest on the part of the truly basic scientist in human experimentation. This will be described in terms of the scientist's goals.

The investigator has many goals, and, in many aspects, they are like those of the practitioner in ultimate aim. The investigator is concerned with health and its preservation and the betterment of life as well as with the causes and consequences of disease, the mechanism and relief of its

symptoms, correction of its signs, prevention of lasting effects of disease, and the very eradication of disease. Activities directed toward these ends involve, very often, alteration of function of the body or the mind, in health or in disease, "directly or indirectly, in individuals or groups, primarily for the advancement of . . . human welfare. Although use of a procedure or its withholding may directly benefit the person involved, its basic purpose is for elucidation and generalization."[6] When possible, investigation begins in animals but finally must be applied to man.

The goals mentioned are ancient ones. There is a new one or, more accurately, a newly recognized one. In the last decade or so, it has become increasingly clear that the study of disease in man can have a deeper meaning than once was believed to be the case. The view was widely held (and still is in some quarters) and the study of disease at the bedside level represents nothing more than applied science at best. A more thoughtful approach could long ago have led to a broader grasp of the situation: some parts of basic scientific advance (I use the term in its classical sense) are utterly dependent on disease. An abundance of examples comes to mind. Pauling's interest in "molecular disease" arose in part from work with abnormal forms of hemoglobin. Although neurophysiologists have long been interested in the biochemistry of the potassium ion, recent basic advances in knowledge of this ion have come from studies of dehydration. Knowledge of the physiology of the endocrine glands is largely indebted to the fundamental leads found in disease. The anatomy of the central nervous system has been learned, in significant part, by study of cerebrovascular accidents. Such diverse matters as the discovery and understanding of vitamins, the development of microbiology, and even the advance of genetics in study of hereditary factors in disease leave no room for doubt that truly basic science can be advanced by a study of disease processes. This awareness leads to a further extension of human experimentation. With these developments it is time to examine the many-faceted problem of experimentation in man.

Ladimer[6] has expressed it thus:

Properly conducted experimentation [in man] by qualified scientists must therefore be considered an integral branch of biologic and medical science, but it does not thereby become customary medical practice. Nor does its essentiality and acceptance establish clearly its character or place the methods employed beyond scrutiny. The responsible professions have a duty to delineate for their own members and for a critically vigilant public the nature of medical research and the limits within which it may be properly undertaken.

These introductory remarks can be concluded with the comment that prevention of experimentation can also be an experiment, even a very dangerous one, as, for example, withholding treatment of a control group. If experimentation is to be withheld, "it should be demonstrated that the proposed experiment is more dangerous or more painful than the known [or probable] results of inaction."[7] This is an expression of an ideal, rather than a practical, possibility in most cases.

Throughout this article the aim has been to present sound background data, common-sense views, and principles of procedure rather than rules. The intricate considerations which must be brought to bear on this general subject leave room for only a few absolute statements. There are discussed in the section on Codes.

Social Necessity

In the foregoing remarks it is clearly evident that human experimentation is essential for the welfare of the race, for in medical research lies "a common benefit not obtainable by other means."[6] The development of medicine, the safeguarding of health, and some types of basic scientific advance all require human experimentation. With the recent Hitlerian acts freshly in mind, it is not surprising that responsible investigators are wary of such phrases as "for the good of society." In any case, the scientist or physician has no right "to choose martyrs for society," as Kety[8] has put it.

It should be apparent that no stigma is attached to the performance of human experiments *per se;* disgrace and infamy can arise only through its misuse. The moral obligation of performing all human experiments, with due regard to the sensibility, welfare, and safety of the subject, must not be violated. As phrased by Claude Bernard in 1856, "Christian morals forbid only one thing, doing ill to one's neighbor." So, among experiments that may be tried on man, those that can only do harm are forbidden, those that are harmless are permissible, and those that may do good are obligatory.[9]

Unfortunately, decision is usually not so simple as this sounds; choice often lies among various shades of gray, not between black and white. The social necessity for experimentation in man operates, of course, only when the desired ends cannot be obtained in other ways, as through experimentation in animals.

Subject

Observations on the choice of a subject can be set down as follows:

1. It is often not possible to directly transfer observations made in normal individuals to the sick. The complexities here are so great that only one or two suggestive examples can be mentioned: (*a*) It is exceptionally difficult, if not impossible, to reproduce usefully in normal subjects symptoms which ordinarily arise in disease. Take, as an example, pain. Beecher[5] has compiled evidence which supports this view, in that 15 groups of investigators attempted but failed to show a dependable relationship in man between pain threshold and the action of analgesic agents, notwithstanding scores of papers to the contrary. (*b*) There is no assurance that the high incidence of nausea in normal individuals after administration of morphine holds true for those who are in pain. Incidentally, this points to a problem not yet satisfactorily solved, that is, how to secure information on the side-effects of therapeutic agents when these side-effects may be similar to those present at times in the disease state studied

2. Individuals who may die suddenly or who seem to be in imminent danger of death should not, under ordinary circumstances, be chosen as subjects for experimentation, however harmless the planned procedure may be. If death occurs during such an experiment, it could cast a shadow over a potentially valuable agent or useful technique, not to mention placing the investigator in a most unhappy predicament, where, although innocent, he may appear guilty.

3. It is usually unwise to study a therapeutic procedure in an individual who has also a disease unrelated to the expected therapeutic effects.

4. Lay subjects, sick or well, are not likely to understand the full implications of complicated procedures even after careful explanation.

To obtain the consent of the patient to a proposed investigation is not in itself enough. Owing to the special relationship of trust which exists between a patient and his doctor, most patients will consent to any proposal that is made. Further, the considerations involved are nearly always so technical as to prevent their being adequately understood by one who is not himself an expert. It must, therefore, be frankly recognized that, for practical purposes, an inescapable responsibility for determining what investigations are, or are not, undertaken on a particular patient will rest with the doctor concerned. Nearly always his judgment will be accepted by the patient as decisive.[10]

Or, as Guttentag[11] has put it, "one has only to think of present-day specialization in medicine in order to realize that the patient is frequently not able to grasp all the implications of a certain procedure so far as his health is concerned."

To some, this complexity leads to a strong admonition concerning voluntary work. At one time, Pfeiffer[12] held the view that one should "never use anyone except a volunteer who is at least at the level of a graduate student and who has investigated for himself the nature and possible

dangers of the drug or procedure involved." Many investigators would not agree with this last view. For some types of investigation, especially when subjective factors are involved, it is essential to have subjects who know nothing about the expected results and have no vested interest in the outcome. Certainly Pfeiffer's early requirement for an informed subject cannot be complied with in the case of the diseased subject. Such difficulties, however, emphasize the increased responsibility of the investigator when the subject cannot truly understand the full implication of the study contemplated. This view is set down in some detail for comparison with this idealistic, yet thoughtful and practical, investigator's current view. Pfeiffer[13] states his present view: "My quotation from 1951 must certainly be modified as of this date since we are using prisoners at the Atlanta Penitentiary who are not graduate students! We do screen our prisoners for psychiatric difficulties by having them complete a Rorschach examination, IQ assay, and MMPI tests. We also go over their psychiatric history very carefully. My statement of 1951 represents the ideal situation rather than the practical situation."

Volunteer

Information Given.—The information given to or obtained by the volunteer subject may vary widely from none at all, when innocuous procedures are undertaken in the study of subjective responses, to full discussion whenever any risk is involved. These matters have been referred to in the preceding section.

Laboratory Personnel and Medical Students.—Laboratory personnel and medical students are often considered legitimate game by the eager but impoverished investigator, and certainly tradition has accepted their use. In my opinion, at least, there are two reasons why such groups are usually not a good choice: 1. In a sense, these are captive groups, not so seriously so as prisoners of war perhaps, but nonetheless available for certain kinds of subtle coercion. A volunteer should be just that, not one who may be subject to fear of the consequences if he does not cooperate. The more domineering the investigator, and thus the more valid the point made, the more likely is this possibility to be disclaimed. Denied or not, the situation does exist; it is better to avoid it. 2. In quantitative studies of subjective responses over many years, it has become clear to me that, in this field at least, subjects must not be in communication with each other, for, if they are, certain false "syndromes" are "established," through conditioning presumably. Lack of space precludes citing some startling examples of this. The hazard to sound conclusion of such action is nowhere more amusingly evident than in the reports of some of those who have studied the effects of psychotomimetic drugs in their own personnel.

Mackintosh,[14] however, has expressed a sound and considerate point of view concerning the use of laboratory personnel:

> **On the difficult question of laboratory personnel, we had certain decisions to make in the London School of Hygiene. In the study of malarial parasites "resting" in the human liver we had offers from a skilled technician to submit himself to infection and then to have a small liver section taken. In this case the technician was a senior man who was fully aware of the risks involved. His offer was gratefully accepted, but at the same time a regulation was passed that in the future no human experiment should be allowed without a full report being made in advance to the School Council (which is the professional body) and to the Board of Management, which has a considerable representation of scientists, and also lay members. The crux of the decision was whether the volunteer had the training and skill to appreciate the whole situation, although not necessarily the details of the procedure. It was evident that there might be subjective matters of study which the volunteer ought not to know beforehand, so as to avoid vitiating the experiment. The additional point of the decision was to make sure that the volunteer gave his consent freely, or, better still, offered his service in writing. In such cases no fee or reward, apart from any out-of-pocket expenses, should be offered.**

Lasagna and von Felsinger[15] have discussed the "ample reason(s) for wariness in making generalizations regarding drug effects from a study, no matter how careful, of any *single* group of individuals, be they sick or healthy, volunteer or non-volunteer."

Civil Prisoners.—The major scientific contributions which have come directly from utilization of civil prisoners who have volunteered for such endeavors offer at least a pragmatic justification for the practice. Possibilities for direct or indirect coercion, flagrant or subtile, are so great that use of these individuals must be considerate indeed to be sure that there has been no coercion. The practice has a rather long history. Included as civil "prisoners" are the inmates of orphanages[16] and asylums for the insane[17] as well as prisoners in jail.[18] During World War II both federal and state prisoners made important contributions to malaria studies, the use of blood plasma, plasma fractions, and plasma substitutes, and trials of various new drugs. In most prisons more volunteers were available than were needed.[2]

The advisory committee[18d] appointed by Governor Green, of Illinois, had this to say:

> **Since one of the purposes of the parole system is reformative, the reformative value of serving as a subject in a medical experiment should be considered. Serving as a subject in a medical experiment is obviously an act of good conduct, is frequently unpleasant and occasionally hazardous and demonstrates a type of social consciousness of high order when performed primarily as a service to society. The extent to which the service of a prisoner in an experiment is motivated by good social consciousness on the one hand and by the desire for a reduction of sentence in prison on the other is a matter for consideration in the case of each prisoner. Regardless of a prisoner's motives for volunteering for an experiment, a habitual criminal or a prisoner who has committed a notorious or heinous crime should not be considered an acceptable volunteer for a medical experiment.**

The rewards for prisoner volunteer service vary all the way from gifts of tobacco [18e] to a full pardon.[18b] Cautioning against excessive rewards, the Green committee said:

> **The most important requirement for the ethical use of human beings as subjects in medical experiments is that they be volunteers. Volunteering exists when a person is able to say "yes" or "no" without fear of being punished or of being deprived of privileges due his in the ordinary course of events.**
>
> **A reduction of sentence in prison, if excessive or drastic, can amount to undue influence. If the sole motive of the prisoner is to contribute to human welfare, any reduction in sentence would be a reward. If the sole motive of the prisoner is to obtain a reduction in sentence, an excessive reduction of sentence which would exercise undue influence in obtaining the consent of prisoners to serve as subjects would be inconsistent with the principle of voluntary participation.**

The committee added the somewhat unrealistic comment: "Obviously no one may make representations to a prisoner concerning the extent and types of reward which may accrue as a result of his service as a subject in a medical experiment." In all examples I have seen, the terms were explicitly stated beforehand and were always lived up to after the fact.

Military Prisoners.—It is never permissible to use prisoners of war for experimentation. This is the sound policy of the Department of Defense.

Volunteer Corps

Hogben and Sim [19] have this to say:

> **If we approach the problem [of human experimentation] against a background in which the major advances of medicine occurred in the social setting of pestilences, practical difficulties of enlisting volunteers without violence to ethical standards are easy to exaggerate; but a wholesome regard for the sanctity of life becomes increasingly less relevant to a statement of the priorities of medicine in western communities with a life-expectation well above 60 years at birth. There is indeed an ever more pressing need for knowledge about many once-thought *minor* evils. We cannot effectively tackle them by group methods; but we might well do so with the help of individuals now willing to risk life or limb on the speedway or in the ascent of Mount Everest, if we could institutionalize a not uncommon appetite for adventure consistent with acceptable moral standards. It is not beyond the reach of social engineering to create a new corps of civil defence with that**

end in view. The voluntary response to the appeal for blood donors disposes of doubts about the feasibility of such an undertaking, if sponsored by an adequately accredited organization.

We have in the United States the beginnings of such a corps in the group of conscientious objectors to military service who volunteer, and also in the Mennonite group of young adults who volunteer as subjects for scientific studies.

Investigator

Characteristics and Qualifications.—The physician and the investigator are different in their procedures, in their aims, and in their immediate ends. To paraphrase Ladimer,[6] the physician accepts patients and is mainly concerned with their welfare; the investigator selects subjects (problems as well as individuals) and, while responsive to the patient's interest, is bent on solving the scientific problem. But "one irresponsible investigator can do great harm to medical science."[20]

All the so-called codes as guides to human experimentation emphasize the necessity that the experimenter be well trained and adequate as a scientist to undertake the study proposed. Medical research, when it involves treatment or any physical procedures beyond the simplest type, requires that the investigator or his close associate be a qualified physician. No other profession gives such prerogatives, and no other profession, probably, presents such a generally high level of unselfishness and compassion. Of these two qualities, unselfishness is the more important for subject and project alike. Imagination, objectivity, and the power to generalize soundly are all essential.

Responsibilities and Safeguards.—Claude Bernard[21] stated the responsibilities of the investigator as follows:

As far as direct applicability to medical practice is concerned, it is quite certain that experiments made on man are always the most conclusive. No one have ever denied it. . . . First, have we a right to perform experiments and vivisections on man? Physicians make therapeutic experiments daily on their patients, and surgeons perform vivisections daily on their subjects. Experiments, then, may be performed on man, but within what limits? It is our duty and our right to perform an experiment on man whenever it can save his life, cure him, or gain him some personal benefit. The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i. e., to the health of others. But performing experiments and operations exclusively from the point of view of the patient's own advantage does not prevent their turning out profitably to science.

Bernard's view cannot soundly be construed as ruling out risk when there is hope of gain; both must be weighed.

In patently nonhazardous experimentation, there is no necessity for the investigator to subject himself first to the experimental procedures. However, whenever doubt exists as to safety, it is advisable for the investigator first to subject himself to the possible hazards involved.

When it is not known whether a given treatment is likely to be effective, the investigator is entitled to withhold it if new and more promising therapy waits trial. However, he is not entitled to withhold therapy when its effectiveness is assured, except with the consent of the patient. Green states it thus: "where the value of a treatment, new or old, is doubtful, there may be a higher moral obligation to test it critically than to continue to prescribe it year-in-year-out with the support merely of custom or wishful thinking."[22] McCance has said: "the medical profession has a responsibility not only for the cure of the sick and for the prevention of disease but for the advancement of knowledge upon which both depend. This . . . responsibility can only be met by investigation and experiment."[20]

Although many differences exist between the practice of medicine and human experimentation, there are, nonetheless, certain parallels that can usefully be drawn in examining one's position of responsibility. In questions of malpractice a legitimate point is whether the actions of the physician were in accordance with generally accepted standards in the given case. So too the same question can be appropriately raised concerning experimentation.

In research, standards must relate to how the investigator proceeded and how he checked himself. The means by which research of high quality has been managed and the safeguards employed to protect the subject can be generalized into a set of precepts similar to that governing malpractice, to serve as a guide. Thus, wilful or negligent deviation, resulting in injury, would constitute a basis for liability. On the other hand, observance of all known precautions, even in the event of an untoward result, would protect the honest, qualified investigator. Neither he nor the physician is a guarantor of success, but each has a responsibility to his own law and credo.6

The responsibilities devolving on those who undertake experimentation in man are so great that, whenever even remote hazard is a possibility, group decision supported by a proper consultative body should be employed.[7] Self-experimentation "without such collaboration and consultation seems as indefensible as similar experimentation on another individual."[7] "At the Clinical Center of the National Institutes of Health, for instance, projects involving deviation from accepted medical practice or unusual hazard are presented in writing to a Clinical Research Committee. Consent is obtained from subjects and final approval from the Center's Medical Board and the Director of the National Institutes of Health."[6] The British Medical Research Council has said:

In any particular case—so specialized has medical knowledge become—only a small group of experienced investigators, who have devoted themselves to this branch of medicine, are likely to be competent to pass an opinion on the advisability of undertaking any particular investigation. But in every branch of medicine such a group of investigators exists. It is upon them, and the specialized scientific societies to which they belong, that the medical profession must mainly rely for the creation of the body of precedents and the climate of opinion which shall guide investigators in clinical research . . . it is incumbent upon the medical scientific societies to accept this responsibility and, by encouraging critical discussion on the communications presented to them, help to resolve doubts and to form a body of opinion of what is necessary, desirable and justifiable to guide investigators in their field.[10]

Wiggers[9] has expressed a similar view.

The Department of Hospitals, City of New York, issued an order in which is stated: "#1 That proposed clinical or laboratory investigations in any hospital or institution of the Department, whether or not under the auspices of affiliated medical schools, be submitted for review and approval by the Executive Committee of the Medical Board of the hospital concerned.

"#2 That unless it is specifically designed to benefit the patient involved—no research using a patient as a subject is permitted in any hospital or institution of the Department."[23]

Relationship Between Subject and Investigator

This relationship very often is identical with the patient-physician relationship and will be considered from that viewpoint. There is good reason why this facet of the human experimentation problem should be considered. Whenever the physician tries out a new drug or a new technique—not necessarily new in any absolute sense, perhaps only new for his particular patient—he is experimenting in his effort to relieve or cure the individual involved.[24] It could often be shown to be wrong to withhold such methods of trial. Such "experimentation" is, in principle, relatively uncomplicated. Great complications arise, however, when the experimentation on one patient is not expected to benefit the immediate patient but is for the good of patients in general. Recent increase in this type of experimentation requires consideration, for such a matter involves the most basic elements in the patient-physician relationship as well as the attitude toward life and its responsibilities of both the patient and the psysician. As Guttentag[11] puts it, "not all experiments performed on men will ever be of value to these particular men. And it is with these breathing men that we are concerned as physicians."

Only physicians can legally take the responsibility for medical experimentation on man. In any case, no one else is so well equipped to carry out work "to conform or disprove a biological generalization with regard to man . . .[than] the

profession that is trained more completely than any other in comprehending the somatic and psychological aspects of human life, be it healthy or diseased." In addition to this reason there is another. As Guttentag[11] points out, it is related to the original patient-physician relationship: "Here *both* the healthy and the sick persons are . . . fellow-companions, partners to conquer a common enemy." Guttentag has called it " 'mutual obligations of equals' or to use Weizsaecker's term, it is 'solidarity.' Objective experimentation to confirm or disprove some doubtful or suggested biological generalization is foreign to this relationship." He considers the physician-experimenter and the physician-friend as two distinct aspects of the doctor.

Against the background of the two roles played by the physician, Guttentag[11] considers three currently evolving developments. First, there is the use of force as exercised in Hitler's Germany. It seems unlikely that this will be of importance in this country, except for extremely rare local abuses, for

> **the overwhelming majority of physician-experimenters, if not thoroughly aware of the nature of the original patient-physician relationship, are so deeply rooted in the democratic spirit that they agree, and will continue to agree, that the use of force is not justified on a single person, even if millions of other lives could be saved by such an act. They realize that as an amoral act from the standpoint of democratic brotherhood, it might create millions of amoral sequels, and that the moral history of mankind is more important than the scientific.**

Second, the use of the "hopelessly incurable" as experimental subjects has developed recently. I have already stated the reasons for my deep conviction that those who are in imminent danger of death should not be subjected to experimentation, except as part of the therapeutic effort for the benefit of the subject himself. Occasionally, reports are found wherein use of the "hopelessly incurable" seems to justify dangerous experimentation. The error in this appears evident. It is not the physician's prerogative to make or to profit from such dubious judgments. The use of such subjects is

> **meant to be noble in the democratic spirit, yet it unconsciously challenges this spirit more subtly but no less than the use of force, because it violates the concept of equality or brotherhood in violating the principle of the original patient-physician relationship, From the experimenter's point of view, the description "hopelessly incurable" is not germane to his purpose. The designation is inadequate, because it does not specify the time element—hopeless within hours, days, months, years? And if months or years are concerned, do all experts agree on the status of their respective sciences and deny the possibility of discovering effective agents within such a period? The term is also unnecessary. . . . From the standpoint of the physician-friend, the assertion is not germane to his purpose, either. To him it is an expression of detachment between physician and patient, the announcement of a scale of partnership *vs.* domination quite contrary to its original spirit. As a matter of fact, it creates the paradox that the healthier the patient, the more he should be the concern of his physician; the sicker, the less.[11]**

Third, "increased technicalities of many problems and procedures" have arisen. To Guttentag[11] this suggests that for the protection of the subject the physician-friend and the physician-experimenter should be two persons, lest selfishness decide the issue. The physician-friend would play the part of attorney for the defense, whereas the physician-experimenter would be the prosecuting attorney. Practically, the physician-friend and the physician-experimenter must sometimes, and often will, be the same person. Nevertheless, it is necessary that the two attitudes be recognized and pondered.

Justification for Human Trial

The importance of the project undertaken must be commensurate with the risk involved. The insurance of this is a cardinal responsibility of all who undertake experimentation in man. However, there is still a vast area where judgment—one hopes sound judgment—must operate. Only the fanatic denies that animal experimentation must precede human experimentation. As Sir Geoffrey Jefferson[25] put it, "Man is too rare, too expensive, altogether too valuable an animal" to be first used in the study of technical procedures or trial of even therapeutic agents. There are, at the same time, species differences. Ultimately, the definitive test must be made in man. Certain types of experimentation are impossible in animals and must be done in man, as discussed in the following section.

Types of Human Experimentation

These classifications can be considered from various points of view. For example, one scheme is based on the patient's role: (1) "passive," in which human tissues or products are examined, as by the pathologist or biochemist; (2) "late active," in which studies are applied to the patient only after prior investigation on animals; and (3) "initial active," in which work must be undertaken exclusively on man.[7] Another classification is based on the purpose of the research; that is, whether it is designed to be of value to the immediate patient under study or to patients in general. Still other categories of consideration are reasonable; for example, whether the investigation is to advance basic science or whether it falls into the realm of applied science.

The reviewer must confess to scant interest in such schemes. There are, however, several points that should be made, points which cut across various classifications.

1. Prior controlled experimentation in animals is absolutely essential whenever this is advantageous, and this is almost always, in one way or another, the case. Even when primary drug effects cannot profitably be studied in animals, possible toxic effects can and should be.

2. In certain circumstances, experimentation in animals is impossible or useless. For example, mental disease and its prodromal states must be studied in man. Studies of subjective responses, symptoms, require human subjects, although useful inferences can be drawn in some cases from animal work, for example, studies of the effect of analgesic agents on animal withdrawal reflexes presumably produced by pain. Since certain syndromes and diseases do not occur in animals, obviously they must be studied in man.

3. Although the investigator should be willing to serve as a subject in any project having even remote possibilities of hazard (as evidence of his good faith), self-experimentation is an unwise performance whenever judgment can enter into the conclusions drawn.

4. Any classification of human experimentation as "for the good of society" is to be viewed with distaste, even alarm. Undoubtedly all sound work has this as its ultimate aim, but such high-flown expressions are not necessary and have been used within recent memory as cover for outrageous ends.

Permissible vs. Nonpermissible Human Experimentation

Very often decision lies between two shades of gray.[26] When hazard is involved, or may be present, group decision by one's peer becomes important. Ivy[2] has presented some telling examples of rash or foolish experimentation. On top of all his other problems, the harassed investigator recognizes that sometimes to prevent an experiment may of itself be also an experiment, even a dangerous one.

Pope Pius XII[27] expressed the stand of the Roman Catholic Church thus:

> **In the domain of . . . science it is an obvious law that the application of new methods to living men must be preceded by research on cadavers or the model of study and experimentation on animals. Sometimes, however, this procedure is found to be impossible, insufficient or not feasible from a practical point of view. In this case, medical research will try to work on its immediate object, the living man, in the interests of science, in the interests of the patient and in the interests of the community. Such a procedure is not to be rejected without further consideration. But you must stop at the limits laid down by the moral principles We have explained.**

Propriety in Publication

When reports on human experimentation are prepared for publication,

It cannot be assumed that it will be evident to every reader that the investigations being described were unobjectionable. Unless such is made unmistakably clear misconceptions can arise. In this connection a special responsibility devolves upon the editors, and editorial boards, of scientific journals. . . . It is desirable that editors and editorial boards, before accepting any communication, should not only satisfy themselves that the appropriate requirements have been fulfilled, but may properly insist that the reader is left in no doubt that such is indeed the case.[10]

There have been instances in which certain details and complications have been deleted from published reports to avoid unfavorable criticism. It seems unlikely that such abuses are common, but when they occur, it is probable that the study should not have been carried out in the first place. The failure to report serious complications in a final report is inexcusable.

Ethical and Moral Aspects

The physician, with his 2,500-year-old traditions and his constant preoccupation with problems of life and death, has understandably had a long concern with ethical matters. The first codification of such matters in the United States occurred in 1848,[28] when the American Medical Association patterned its statement on Sir Thomas Percival's "Medical Ethics" of 1803. The principal categories concerned the relationship of the physician to society, to his patient, and to his colleagues.

There have been a good many controversies involving medical ethics in the past 20 years. Fitts and Fitts[29] have suggested as various causes for this the splintering of medical knowledge into numerous specialties, leading as it does to group practice; the spread of insurance schemes, with intrusion of the third party between the physician and his patient; and finally "the radical treatment of serious disease, which appears, when first applied, to verge dangerously upon human experimentation." The implication of this last comment, i.e., the radical treatment of disease, however close to the legal stand it may be, is possibly at variance with present widespread humanitarian concepts.

Changes in ethical consideration may be slow, but they do occur and are illustrated in correspondence to the Royal Society in England. In 1756, Sir Hans Sloane described how,

The princess Anne, now princess royal of Orange, falling ill of the small-pox in such a dangerous way that I very much feared her life, the late Queen Caroline, when princess of Wales, to secure her other children, and for the common good, begged the lives of six condemned criminals, who had not had the small-pox, in order to try the experiment of inoculation upon them. But Mr. Maitland, who had inoculated at Constantinople, declining for some reasons to perform the operation. . . . [but later he was persuaded and] undertook the operation, which succeeded in all but one, who had the matter of the small-pox put up her nose, which produced no distemper, but gave great uneasiness to the poor woman. . . . To make a further tryal, the late Queen Caroline procured half a dozen of the charity-children belonging to St. James' parish, who were inoculated, and all of them, except one (who had had the small-pox before, tho' she pretended not, for the sake of the reward) went thro' it with the symptoms of a favourable kind of that distemper.

The very fact that such a performance on the part of the present royal family of Great Britain would be unthinkable emphasizes the change.

This ethical change is further exemplified in recent correspondence to *Lancet*, in which the discussion, even though pros and cons are presented, indicates a lively conscience. In the letter which started this correspondence, Fisher[30] had this to say:

It is a matter for regret that the use of normal children (or children suffering from some irrelevant disease) as controls in clinical research appears to be increasing.

No medical procedure involving the slightest risk or accompanied by the slightest physical or mental pain may be inflicted on a child for experimental purposes unless there is a reasonable chance, or at least a hope, that the child may benefit thereby.

If this is true—and I hope that there are few doctors in this country who would disagree—then it must surely be difficult to justify the use of two hydrocephalic infants reported in the paper by Dr. Doxiadis and his colleagues, and the use of a normal control by Dr. Bickel and his colleagues.

It may be, of course, that there were some good reasons for the use of these children which have not been made clear.

Holt[31] replied for one group of authors:

It is quite reasonable that Dr. Fisher should raise the question of the use of normal children or children suffering from some irrelevant disease as controls in clinical research. There are extreme opinions on both sides, but I feel most of us adopt a policy between the two—somewhere in the grey between the rather theoretical white and black. My own working policy, which differs slightly from that expounded by Dr. Fisher in the second paragraph of his letter, is that no procedure should be carried out involving risk or discomfort without a reasonable chance of benefit to that child *or other children;* and this principle was followed throughout our work. The crux of the matter is contained in the last sentence of Dr. Fisher's letter—we owe it to ourselves to explain our actions. Surely we all weigh these matters most carefully in our own consciences.

Further comment was made by Bickel and Gerrard:[32] "We are grateful to Dr. Fisher for raising a problem of which we are fully conscious in our daily work. Nevertheless, errors of metabolism constituting the underlying cause of many diseases cannot be understood or properly treated without knowledge of normal physiology."

Leys[33] commented on the previous correspondence:

The privileged position which doctors hold in society depends entirely on the trust which people have in the purity of their motives. This is stated explicitly in the international code adopted by the World Medical Association in 1949: "Under no circumstances is a doctor permitted to do anything which would weaken the physical or mental resistance of a human being except from strictly therapeutic or prophylactic indications imposed in the interests of the patient." There is no justification here for risking an injury to an individual for the possible benefit to other people, as enunciated by Dr. Holt as his guiding principle. Such a rule would open the door wide to perversions of practice, even such as were inflicted by Nazi doctors on concentration-camp prisoners. The magnitude and crudity of their "experiments" must not be allowed to blunt sensitivity to breaches of the medical ethic made on a smaller scale and with greater plausibility. Of this nature are experiments performed upon condemned criminals, with or without the victim's consent, upon conscientious objectors to military service, upon persons with chronic mental illness or deficiency or incurable disease of any kind, and all procedures, whether therapeutic in intent or not, which are not designed with the sole intention of improving the lot of the individual upon whom they are performed. Only one exception can be allowed—i.e., when the experimental subject is an adult whose judgment is not impaired and who freely gives his consent. No child must ever be the subject of such an experiment.

It is clear that the assumption by doctors of scientific methods and techniques calls for critical examination of the uses to which these methods are put. The scientific material of the clinical research-worker is human life.

I should like to see a resumption of the practice by which all doctors upon qualification were required to make a declaration of adherence to the medical ethic. There is need for a revised, more simple form of the Hippocratic oath, relevant to the circumstances of the 20th century. For some time the ethics subcommittee of the Medical Association for Prevention of War has been occupied with such a revision, and I give, for the sake of discussion, the tentative and interim results of this attempt.

Items (2) and (4) of the revised oath are pertinent to the present discussion:

(2) To direct all my work to the preservation of life and the relief of suffering, and under no circumstances whatever to use my medical knowledge to harm any person, nor take part in any experiment involving risk of injury, without assuring myself of the understanding and freely given consent of an adult subject, nor without consulting my colleagues upon the value and necessity for such an experiment.

(4) To communicate freely to all doctors any discoveries which I believe myself to have made concerning the nature, cure or prevention of disease.

Ethical and moral implications and problems surround every facet of experimentation in man. This has been evident in each of the preceding sections of this report. The central conclusion is that it is unethical and immoral to carry out potentially dangerous experiments without the subject's knowledge and permission. Every act of a physician designed soundly to relieve or cure a given patient

is experimentation of an easily justifiable kind. The patient's placement of himself in the physician's hands is evidence of consent. The problem becomes a knotty one when the acts of the physician are directed not toward benefit of the patient present but toward patients in general. Such action requires the explicit consent of the informed patient. It also requires more than this—it requires profound thought and consideration on the part of the physician, for the complexities of medicine are, in some cases, so great that it is not reasonable to expect that the patient can be adequately informed as to the full implications of what his consent means. His trust in the physician may lead him too easily to say yes.[34] Although there is no excuse for failure to do one's best to present an accurately informative picture to the subject, it is an injunction to the experimenter himself to cultivate a deep sense of his own responsibility in such a case.

"The patient, however humble and however ill, in whatever degree derelict and forlorn, has sacred rights which the physician must always put ahead of his burning curiosity."[3] The situation is a safer one, as Guttentag points out, when the "physician-friend" who looks after the patient's illness and welfare in general is not the same person as the "physician-experimenter."

"The ethical principles involved in the use of the mentally incompetent are the same as for mentally competent persons. The only difference involves the matter of consent. Since mental cases are likened to children in an ethical and legal sense, the consent of the guardian is required."[2]

The ethics and practice of placebo therapy have been reviewed and discussed in considerable detail by Leslie[35] who concluded, "The proper use of the placebo requires, in addition to broad medical knowledge, a depth of human understanding not requisite to the purely materialistic approach to medicine."

In a speech delivered on Sept. 14, 1952, Pope Pius XII[27] discussed the moral limits of medical research and treatment and, in particular, the interests of science as justification for research and the use of new methods. If a procedure "cannot be used without injuring the rights of others or without violating some moral rule of absolute value . . . morally the method is not admissible," even though knowledge might be increased by its use. The reason for this is that, just as science is not the highest good, so also the desire for scientific growth cannot override certain moral values. "Science itself, therefore, as well as its research and acquisition, must be inserted in the order of values."

Further discussion by the Pope concerned the interests of the patient as justification of new medical methods of research and treatment. The physician's rights or power over the patient or subject are only those given by the subject, bearing in mind that "the patient cannot confer rights he does not possess." According to this philosophy, "The patient, then, has no right to involve his physical or psychic integrity in medical experiments or research when they entail serious destruction, mutilation, wounds or perils."

A third interest is the *bonum commune* or common good. The two interests already discussed, that of science and that of the patient, are closely allied to the general interest. This leads to the question, "Can public authority, on which rests responsibility for the common good, give the doctor the power to experiment on the individual in the interests of science and the community in order to discover and try out new methods and procedures?" The answer is obviously "no,"[27] for the individual must not be subordinated to the community; the community exists for the man.

Legal Considerations

The legal considerations surrounding human experimentation have been exhaustively reviewed and documented by Ladimer.[36] Appropriate to the present report is a statement of the basic assumptions and general principles involved. In addition to this, attention will be called to some surprising lacks of legal precedent in this field.

The practice of medicine has been described over some thousands of years in recorded history, and during this vast period it has been hedged about with innumerable oaths, precedents, customs, rules, orders, and laws for the protection of the patient. Human experimentation is as ancient as the practice of medicine; yet, remarkably enough, no specified legal precedents have been set down to protect the subject or the investigator. At the same time there is abundance of precedent to indicate that, however able, skillful, conscientious, well trained, and generally well qualified the investigator is, he experiments on man to his peril. The first malpractice suit involving alleged experimentation occurred in 1767, *Slater* v. *Baker*. It "established the rule that experimentation was at the physician's peril,"[36a] although the court commented at the time on the surgeon's good character and repute.

As Ladimer[36a] has put it, the position taken by strict legal writers and jurists who have summarized the issue's present position is as follows: In treating the patient "there must be no experimentation . . . we find that legal encyclopedias have unwaveringly set forth that while it is the duty of the physician or surgeon to keep up with advancements in his profession, it is also his duty not to try to forge ahead of it by trying experiments." The doctrine is: "The physician experiments at his peril." Many similar examples could be given. In this seemingly harsh stand "the law" seems to close its eyes to reality, for, as every able physican knows, the adequate practice of medicine involves continual experimentation. No two patients respond precisely alike to any therapeutic procedure. Even in ordinary practice the able physician experiments until his treatment is successful or the patient dies.

The precedent in interpretations just mentioned have to do with the comparatively simple situation of experimentation designed to benefit the immediate patient. The important but much more difficult situation remains, and is scarcely mentioned in legal discussion, in which the research is not designed to benefit the immediate patient but rather patients in general.

To a layman like myself, this is an instance in which the law and its interpretation are far removed from actual practices and from current, universally accepted ethical and moral concepts of Western civilization.[36a] These concepts can be summarized as follows: 1. Progress in the medical sciences depends upon research. 2. Much of this research requires human experimentation. 3. Human experimentation is necessary and proper. 4. It is not considered just that a man be placed in jeopardy or penalized for helping his brother.

The need for a redefinition of human experimentation becomes apparent, because many court rulings equate experimentation with "rash action" and "ignorant and unskillful departure from approved methods." The low esteem of the court for such experimentation is expressed in such phrases as "rash or experimental methods," "mere experiment," or "reckless experiment." By no means could all the acts so castigated be labeled as foolish, nor were they always the work of incompetents. The remarks quoted, "quite typical in cases of this kind reveal[s] the association in the judicial mind between experimentation and professional disregard or negligence. Needless to say, this represents either a complete misconception of scientific experimentation or the singular use of the term so that it partakes of reckless behavior or quackery. . . . The term 'experimentation' has been used loosely by the courts," so says Doctor of Jurisprudence Ladimer, as I would scarcely dare to do. He points out that the precedents, the cases of record, have "dealt not with major problems baffling to medicine and science on which basic research or applied clinical study was required, but with questions which confront the regular practitioner."

In his superb review Ladimer[36a] has said:

The term "experimentation" must be considered objectively (preferably discarded if it retains the connotation of improper medical practice) so that it is recognizable as a

legitimate scientific endeavor which can be advanced by the recognized research scientist. The legal issue would then become not experimentation versus accepted practice of the art of medicine but an evaluation of the plan and conduct of research in relation to specific fact situations, that is, whether the research was conducted with due regard to the interests of the subject. The law has a duty to comprehend the scope and elements of diverse human activity and their places in society if it is to assist in making individual judgments and setting or recognizing general values. . . . Essentially, medical research on human beings consists in experimentation, that is, deliberately inducing or altering body or mental functions, directly or indirectly, in individuals or in groups primarily for the advancement of health, science and human welfare.

Continuing Ladimer[36a] has maintained that medical research

is significantly different from medical practice in such respects as purpose and attitudes, scientific problems or medical hypothesis, study design or treatment, relative obligations of physician-researcher and patient-subject and general environment including scientific staff, facilities and types of clinical material selected. . . The conduct of medical practice, generally conceived to be diagnosis, treatment and care, is governed by the state statute and supporting administrative licensing and regulatory bodies. Medical research on human subjects, except as it is an inherent but not predominant incident of such practice, would appear to be outside the scope of [medical practice]. . . . There is no existing broad police power statute for control of human research although it is, by its nature, subject to the general police power.

Human research "today warrants [legal] recognition as a separate endeavor affected with a public interest as significant as medical practice itself."

Codes

As already mentioned, it is not my view that many rules can be laid down to govern experimentation in man. In most cases, these are more likely to do harm than good. Rules are not going to curb the unscrupulous. Such abuses as have occurred are usually due to ignorance and inexperience. The most effective protection for all concerned depends upon a recognition and an understanding of the various aspects of the problem. Eventually, the broad gap between the law of the land and its interpretation, on the one hand, and scientifically, ethically, and morally sanctioned experimentation in man, on the other hand, must be narrowed, if not closed. This legal development can be helpful and directed toward progress or can be harmfully restrictive. Which it shall be will be determined by the breadth of understanding expended on this complex subject.

Since only physicians can accept the responsibility for human experimentation, beyond the simplest procedures, the oath of Hippocrates has been a basic guide. The physician agrees to work to the best of his ability for the good of his patients and to "abstain from whatever is deleterious and mischievous." As Claude Bernard[21] put it a century ago: In the field of experimentation "Christian morals forbid only one thing, doing ill to one's neighbor." In terms of principle, these elevated sentiments possibly say all that is necessary. The writer, in common with many other investigators, has sought a practical spelling-out of the principle involved. Various attempts to do this will now be described, using as the basic framework for discussion the 10 points developed at the Nuremberg Military Tribunals.[37]

Nuremberg Code's 10 Points.—It is puzzling to me, as a layman in legal matters, why the opinions expressed and the judgments rendered by the Nuremberg Military Tribunals concerning human experimentation cannot be construed as legal precedents (evidently not the case, cf. Ladimer[36a]) when they say that "certain basic principles must be observed in order to satisfy moral, ethical and legal concepts." At any rate, violation of these principles was considered as sufficient basis for imposing seven death sentences and nine prison terms. It would not seem unreasonable to conclude that, if "certain basic principles" (to be stated) are "satisfied," then "legality" shall have been attained. However that may be, the principles and the discussion of them are as follows.[37]

Nuremberg Rule 1: ***The voluntary consent of the human subject is absolutely essential.***

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his heath or person which may possibly come from his participation in the experiments.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

On first reading, this sounds simple, straightforward, and absolutely to the point. Reflection reveals certain difficulties. For one thing, a rigid interpretation of this would effectively cripple, if not eliminate, most research in the field of mental disease, which is one of the two or three greatest medical problems. However, Ivy served as chief medical consultant to the War Crimes Trials and presumably had a hand in formulating the 10 points. As he has said previously: "The ethical principles involved in the use of the mentally incompentent are the same as for mentally competent persons. The only difference involves the matter of consent. Since mental cases are likened to children in an ethical and legal sense, the consent of the guardian is required."[2] If this were the intention of the Nuremberg Tribunal, it is regrettable that the matter was not explicitly stated, for more and more the 10 points are referred to as a sort of Western credo.

We can consider what may be other difficulties in the way of widespread acceptance, difficulties not with the spirit and principal substance of the 10 points but difficulties, nonetheless, of interpretation.

Strict observance of point one would cast considerable doubt not only on the propriety of studying mental disease but also on the use of placebos, essential to progress in studies in which judgment is involved in decision.[38] Explicit observance of point one would require detailed explanation to the participating subject with the inevitable result that he would become self-conscious and introspective. An abundance of evidence in the field of study of subjective responses has shown that such introspection has produced misleading results.[5] The use of placebos in therapy, occasionally necessary for the guidance of the able, responsible physician as well as the treatment of the patient, could hardly be tolerated under a strict observance of the point in question.[9]

Furthermore, how is the investigator to draw a practical line in the prior information to be given his patient, between "reasonably to be expected" and possible hazards, when these will often be quite unknown in first experiments? Kety's[8] discussion of this question is, as usual, to the point:

In studies on normal individuals where there was no intent or little possibility of helping the subject, the rule of voluntary consent is, of course, absolutely essential and the necessity of complete explanation equally important. The completeness of the explanation, however, need refer only to that information which will enable the subject to make a judgment upon hazards and need not include other scientific information irrelevant to the question of risk and knowledge of which on the part of the subject may be prejudicial to a controlled experiment. In other words, if one were giving a potent drug or a placebo, it would be necessary to explain to the subject only the risks involved in the taking of the drug. In the case of patients there are important justifications for clinical research in addition to those which hold for normal controls. In the first place, if the research is relevant to the clinical condition from which the patient is suffering, and I feel that it should be, there is the clear possibility of personal benefit to the patient from the research itself, and there, perhaps, the criterion might be the

chance of harming the patient versus the chance of helping him. Even though both of these chances may be low, in most clinical research the chance of personal benefit is usually considerably greater than the chance of harm to the individual patient.

With regard to the justification for using a placebo instead of a drug in the treatment of a disease, this can, of course, be justified if the purpose of the study is to evaluate a new and untried drug, since one can hardly be criticized for withholding an agent of unknown potential for good or harm. With regard to the question of withholding a drug of known benefit temporarily, the concept of greater harm versus greater good to the patient may still apply, in addition to which it may be perfectly possible to get the voluntary consent of the patient to cooperate in a research problem in which certain parts of the treatment may be delayed or withheld temporarily in order to make certain observations. In fact, in any case where the element of hazard is greater than the chances of benefit, the patient may still consent with full knowledge of the risk.

When a patient places himself in the hands of a physician for relief or cure of a symptom or disease, this act implies consent to the physician to carry out the necessary acceptable means to relieve or cure. If the problem is pain, for example, we know that a placebo will often relieve one-half to two-thirds of the pain relievable with an optimal dose of morphine.[39] Surely it would be carrying matters too far to require a dissertation to the patient on grades or degrees of relief anticipated, when real value could be expected from the use of a placebo. Such use of a placebo could reveal, for example, whether a powerful narcotic was actually necessary or not.

Possibly in the beginning, before its power to relieve was established, the use of a placebo in such work might have been challenged on ethical grounds more effectively than at present. This is true of many, if not most, standard therapeutic procedures in wide use today. In the early days of cardiac catheterization, that procedure could have been challenged on serious grounds as jeopardizing the immediate subject's life. Subsequently this has indeed been proved at times to be the case. At present, it is widely recognized that the demonstrated value of the technique outweighs the risk and this has been recognized by the award of a Nobel prize. Ladimer[36a] has described in chilling detail the probable fate in a court of law of the conscientious but bold investigator who takes such risks and experiences his failures early. In most cases, neither true risk nor benefit can be known early, and therefore they cannot be adequately described.

It is easy enough to say, as point one does, that the subject "should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision." Practically, this is often quite impossible, as we have seen, for the complexities of essential medical research have reached the point where the full implications and possible hazards cannot always be known to anyone and are often communicable only to a few informed investigators and sometimes not even them. Certainly the full implications of work to be done are often not really communicable to lay subjects. As mentioned in an earlier section, this throws a serious burden on the responsible investigator. Once again, point one states a requirement very often impossible of fulfillment.

A further limitation on the matter of consent, as viewed by the Roman Catholic Church, has been expressed by Pope Pius XII[27]:

> In the first place it must be assumed that, as a private person, the doctor can take no measure or try no course of action without the consent of the patient. The doctor has no other rights or power over the patient than those which the latter gives him, explicitly or implicitly and tacitly. On his side, the patient cannot confer rights he does not possess. In this discussion the decisive point is the moral licitness of the right a patient has to dispose of himself. Here is the moral limit to the doctor's action taken with the consent of the patient.
>
> As for the patient, he is not absolute master of himself, of his body or of his soul. He cannot, therefore, freely dispose of himself as he pleases. Even the reason for which he acts is of itself neither sufficient nor determining. The patient is bound to the imminent teleology laid down by nature. He has the right of *use*, limited by natural finality, of the faculties and powers of his human nature. Because he is a user and not a proprietor, he does not have unlimited power to destroy or mutilate his body and its functions. Nevertheless, by virtue of the principle of totality, by virtue of his right to use the services of his organism as a whole, the patient can allow individual parts to be destroyed or mutilated when and to the extent necessary for the good of his being as a whole. He may do so to ensure his being's existence and to avoid or, naturally, to repair serious and lasting damage which cannot otherwise be avoided or repaired.
>
> The patient, then, has no right to involve his physical or psychic integrity in medical experiments or research when they entail serious destruction, mutilation, wounds or perils.
>
> Moreover, in exercising his right to dispose of himself, his faculties and his organs, the individual must observe the hierarchy of the orders of values—or within a single order of values, the hierarchy of particular rights—insofar as the rules of morality demand. Thus, for example, a man cannot perform on himself or allow doctors to perform acts of a physical or somatic nature which doubtless relieve heavy physical or psychic burdens or infirmities, but which bring about at the same time permanent abolition or considerable and durable diminution of his freedom, that is, of his human personality in its typical and characteristic function. Such an act degrades a man to the level of a being reacting only to acquire reflexes or to a living automaton. The moral law does not allow such a reversal of values. Here it sets up its limits of the "medical interests of the patient."

Brig Gen. Telford Taylor,[40] who served as chief counsel for the prosecution of war criminals, says of the 10 points from the Nuremberg Trials that "the judgment lays down ten standards to which physicians must conform." Must? Most investigators would if they always knew how. Some of the foregoing discussion might be labeled as quibbling, but some is not. "The law is not concerned with trifles." It is at times difficult to distinguish between the two in a matter of this kind. Nothing said in this discussion should be construed as an attack on the principle of consent. The discussion is set down to indicate that even the "obvious" matter of consent is not so easy to live up to as it sounds.

Nuremberg Rule 2: ***The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.***

The somewhat unsavory nature of the phrase "for the good of society" has been discussed previously. Point two is vague and frowns on random experiments; however, anesthesia, x-rays, radium, and penicillin, to mention a few products of "random" experimentation, seem to justify the disallowed approach. Most of the epoch-making discoveries in science have been unexpected.[41] Surely there is something to be said for the "random" experiment. I, at least, would not know how to define experiments "unnecessary in nature." Doubtless cardiac catheterization and frontal lobotomy would each have been placed in such at category at the beginning of their use. Perhaps lobotomy would be characterized by many in this way now, although it would not have been a few years ago. Decision is difficult; experiment clearly perilous.

Nuremberg Rule 3: ***The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.***

But if the anticipated results fail to justify the performance of the experiment, has the investigator necessarily been guilty of wrong behavior? Who can guarantee the success of any new experiment?

The aforementioned comments are by no means intended to scoff at this valiant effort to codify permissible experimentation in man: They are intended, rather, to indicate more clearly than the 10 points do how difficult it is to be precise in this field. The remaining seven points will be set down without comment.

Nuremberg Rule 4: ***The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.***

Nuremberg Rule 5: *No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.*

Nuremberg Rule 6: *The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.*

Nuremberg Rule 7: *Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.*

Nuremberg Rule 8: *The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.*

Nuremberg Rule 9: *During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.*

Nuremberg Rule 10: *During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.*

Notwithstanding the difficulties of formulating rules to cover all occasions, it was clear from the principles set down at Nuremberg[37] that during the war

these ten principles were much more frequently honored in their breach than in their observance. Many of the concentration camp inmates who were the victims of these atrocities were citizens of countries other than the German Reich. They were non-German nationals, including Jews and "asocial persons," both prisoners of war and civilians, who had been imprisoned and forced to submit to these tortures and barbarities without so much as a semblance of trial. In every single instance appearing in the record, subjects were used who did not consent to the experiments; indeed, as to some experiments, it is not even contended by the defendants that the subjects occupied the status of volunteers. In no case was the experimental subject at liberty of his own free choice to withdraw from any experiment. In many cases experiments were performed by unqualified persons; were conducted at random for no adequate scientific reason, and under revolting physical conditions. All of the experiments were conducted with unnecessary suffering and injury and but very little, if any, precautions were taken to protect or safeguard the human subjects from the possibilities of injury, disability, or death. In every one of the experiments the subjects experienced extreme pain or torture, and in most of them they suffered permanent injury, mutilation, or death, either as a direct result of the experiments or because of lack of adequate follow-up care.

Declarations of Geneva and Rome.—The declarations of Geneva and Rome, which have been adopted by the World Medical Association, consist of a rephrasing and amplification of the Hippocratic oath.[42] Nothing is said directly about experimentation; however, in the section on "Duties of Doctors in General," the following statement could be considered as a limitation of experimentation: "Under no circumstances is a doctor permitted to do anything that would weaken the physical or mental resistance of a human being, except for strictly therapeutic or prophylactic indications imposed in the interest of the patient."

Views of the United States Public Health Service.—The United States Public Health Service has, in effect, adopted the Nuremberg Code's 10 points, with added comment on the importance of group review and group approval of all procedures when even remote possibilities for hazard exist.[7] The rights and welfare of the patient are emphasized.

Concerning research patients at the Clinical Center for Medical Research of the United States Public Health Service, Topping[43] has said:

An overriding principle governing our clinical studies is that the welfare of individual human beings takes precedence over every other consideration. Medical procedures or therapy substantially different from accepted general medical practices are often an essential component of clinical medical research. This offers the only means of acquiring certain information necessary to solve the problems of the diseases and disorders that afflict man. Ethical and scientific considerations dictate, however, that these investigations must be undertaken only after mature thought, under rigorously defined and controlled conditions, and under circumstances that will minimize the dangers of predictable or unpredictable hazards. The basic principle on which all such investigations must rest is that human beings have inalienable rights that supersede all other considerations that may be raised in the name either of science or of the general public welfare. The responsibility of the physician for the physical and mental well-being of persons in his care and for observance of the ethics of his profession cannot be overridden by any element of study or research that is interjected into the relationship between the physician or surgeon and persons in his care.

Views of French Academies.—The National Academy of Medicine, of France,[44] points to the need for a distinction between (1) investigation and therapy directed toward the patient's health as the right and duty of the physician, "conducted with the necessary prudence and following the rules of medical ethics," and (2) research with other ends in view. In this case, in which the experimentation is "for scientific purposes only" it is essential that (1) only true volunteers who are informed concerning the project be used and that (2) the investigators be well qualified for the task at hand and thus reduce the hazard to a minimum.

The view of the French Academy of Moral and Political Sciences is that only responsible, experienced scientists should engage in human experimentation, men who can be expected to draw their own prudent limits to their activities, for written law of itself cannot provide an adequate safeguard. The final justification for such work is the scientific knowledge gained.[45]

British Views.—British views on this subject have been stated by J. M. Mackintosh,[46] a British scientist acting as special consultant to the United States Public Health Service. He has made the following points: Consent is essential by the individual or his guardian.

The law in England is by no means clear as to the responsibility of the experimenter in the case of accident arising. The maxim "volenti non fit injuria" still holds, and might be freely expressed as "volunteers can't claim damages." But, of course, experimental research on sick persons designed to elucidate the nature of their disease and to provide treatment is well established. There has been a movement of late, however, to invite sick persons to cooperate in physical experiments upon themselves with the primary object of elucidating some fundamental problem of disease, without necessarily affecting their individual treatment. [Mackintosh points out that the consent] of a patient as a member of a research team acting as it were the part of the donor in the experiment, is new and startling. . . . Whether this cooperation in the event of accident is covered by the consent in writing of the patient is a matter which would have to be tested in the courts. Obviously the patient would be protected in common law here, as elsewhere, against negligence. But suppose no negligence has occurred, and in consequence of an experiment—the outcome of which cannot be known—a patient suffers a damage or death. The position of the director of the team and of its members would stand in some doubt. It is clear that the law would have to require 1) that the patient had been clearly informed of the nature and purpose of the experiment and of any results that it might involve; 2) that the experiment had been carried out not merely without negligence but with every available precaution against disaster, (e.g., by the provision of restorative apparatus); and 3) that the person responsible for the experiment was a person who could in the eyes of the law be confidently entrusted with the important tasks which he was undertaking. In this respect, it is evident that in addition to any expertly qualified scientist, a physician of standing would have to subscribe to the responsibility of the team.

Mackintosh[46] recognizes two ways of safeguarding the patient after the aforementioned propositions are accepted. This can be either by "an elaborate and meticulously worded code of regulations designed to cover the whole pattern of situations which might occur," or, abandoning any attempt to use a code of regulations, by the use of a "carefully worded 'statement of faith' on the ethical question of research." He expresses as his personal view that "the mere preparation of a closely defined code of regulations would defeat its own purpose. Human beings are not alike, and a code of regulations obeyed to the letter by one research worker might well result in irretrievable damage of a patient. There is no code that could cover the frailties of an inefficient worker, or the sinister vagaries of a research student who placed his own ambitions above the human needs and rights of the patient."

The British Medical Research Council[10] has also said, "it is impossible to frame a code of general advice which would adequately cover the ever changing circumstances which arise."

Views of the Roman Catholic Church.—Pope Pius XII[27] has said:

> Sometimes it happens that a method cannot be used without injuring the rights of others or without violating some moral rule of absolute value. In such a case, although one rightly envisages and pursues the increase of knowledge, morally the method is not admissible. Why not? Because science is not the highest value, that to which all other orders of values—or in the same order of value, all particular values—should be subordinated. Science itself, therefore, as well as its research and acquisitions, must be inserted in the order of values. Here there are well defined limits which even medical science cannot transgress without violating higher moral rules. The confidential relations between doctor and patient, the personal right of the patient to the life of his body and soul in its psychic and moral integrity are just some of the many values superior to scientific interest. This point will become more obvious as we proceed.
>
> Without doubt, before giving moral authorization to the use of new methods, one cannot ask that any danger or any risk be excluded. That would exceed human possibilities, paralyze all serious scientific research and very frequently be to the detriment of the patient. In these cases the weighing of the danger must be left to the judgment of the tried and competent doctor. Nevertheless, as Our explanation has shown, there is a degree of danger that morality cannot allow. In doubtful cases, when means already known have failed, it may happen that a new method still insufficiently tried offers, together with very dangerous elements, appreciable chances of success. If the patient gives his consent, the use of the procedure in question is licit. But this way of acting cannot be upheld as a line of conduct in normal cases.
>
> People will perhaps object that the ideas set forth here present a serious obstacle to scientific research and work. Nevertheless, the limits We have outlined are not by definition an obstacle to progress. The field of medicine cannot be different in this respect from other fields of man's research, investigations and work. The great moral demands force the impetuous flow of human thought and will to flow, like water from the mountains, into certain channels. They contain the flow to increase its efficiency and usefulness. They dam it so that it does not overflow and cause ravages that can never be compensated for by the special good it seeks. In appearance, moral demands are a brake. In fact, they contribute to the best and most beautiful of what man has produced for science, the individual and the community.

Requirements of the American Medical Association.—The American Medical Association[18a] has three principal requirements: "(1) the voluntary consent of the person on whom the experiment is to be performed; (2) the danger of each experiment must be previously investigated by animal experimentation, and (3) the experiment must be performed under proper medical protection and management." This is, in essence, similar to the Nuremberg document, and the comments appended to that are pertinent here.

Wiggers' Statement.—In effect, Wiggers[9] restated the 10 points of the Nuremberg Code, with extensions or additions as follows:

> 1. Human experiments should not be projected until their necessity has been unquestionably established and a feasible humane procedure for their conduct has been formulated.
>
> 2. The scientific, ethical, and legal considerations pertaining to contemplated studies on human subjects should, whenever possible, be reviewed and approved by a group of colleagues who will not participate in the investigation. The nature of the experiments and reasons for their performance should be explained.
>
> 8. The investigation should be so conducted that legal liability under malpractice or personal injury laws never comes into question.

To follow Wiggers' point one concerning necessity would, of course, be proper if danger attended the proposal. In experiments devoid of hazard it is difficult to see why the experimenter should not have freedom to try out his hunches, provided that the subjects understand the uncertain nature of the project and give consent. Many of the great discoveries of science have come from just such "unnecessary" and "random" experimentation.[41] Regarding point eight, as the laws are now written and at present interpreted,[36a] it seems clear that the investigator is frequently, if not always, in danger of being subjected to "legal liability under malpractice or personal injury laws."

World Medical Association.—The World Medical Association has presented a summary of a long report prepared by the Public Health Council of the Netherlands, which was submitted to that country's Minister of Social Affairs and Health on Oct. 10, 1955. After defining human experimentation as any "intervention in the psychic and/or somatic integrity of man which exceeds in nature or extent those in common practice," the report presents an elaborating discussion and summary of reasonable practices already discussed.

> *Approval of the Subject.* It is generally agreed that if the experiment is not solely, primarily, or to any degree a direct benefit to the subject, his approval is required. This approval should neither be conditioned by idealistic impulses, (nurses and medical students); nor by special conditions, (prisoners, etc.). Even under ideal conditions, the subject's consent has only relative importance.
>
> However the committee felt that when a physician undertakes "new treatment" on his own patient, the relationship of confidence between physician and patient is in no way violated if the physician increases his knowledge or experience without first informing the patient, with the understanding that recovery is not delayed and there is no deterimental effect.
>
> After all, hospitals exist not only to treat patients, but also to increase medical knowledge and skill. Animal experimentation always precedes that on humans. The public should understand that the interests of the patients require a certain amount of experimentation.
>
> *Risk.* "Risk" is defined as "any danger that is greater than the inevitable peril." Surgical procedures inevitably involve a risk, therefore, proper investigation and use of powerful new medicaments cannot be carried out without a degree of inevitable risk to the patient.
>
> A distinction is made between the research expert and the investigator who is also the patient's attending physician. The Committee was of the opinion that "medical activities involving risk to the experimental subject should not be carried on by the practicing physician; the practicing physician who also is the investigator is not the person qualified to objectively judge the risk involved."
>
> When experimentation is conducted in institutions such as homes for children, convalescents or old people, etc., the responsibility must be shared by the attending physician in addition to the investigator.
>
> The Committee recognizes the inherent right of a person to accept a voluntary risk, and the right of the investigator to make use of this attitude to achieve altruistic objectives but ethics must act as a check whenever a great risk is involved. Dangerous experiments are never justifiable if the aim is only advancement of medical knowledge; they must also entail some benefit for humanity.
>
> The Committee recognized that in time of war or epidemic, dangerous experiments may be justified. However, in normal times, "human experiments involving dangerous risks of life cannot be reconciled with the nature and objective of the medical profession." Hence it recognized that the nature of this problem does not make it possible to have clearly defined standards governing experimentation; "the conscience of the investigator will have to determine the course of conduct" and even the "individual conscience cannot be relied upon unconditionally." . . . For, "scientific experimentations demand from the investigator an objective attitude, a certain distance and restraint toward his object of experimentation which is actually in conflict with the relationship of physician and patient."
>
> *Standards.* Nevertheless, it is felt that standards should be sought that will govern individual conscience in making decisions; guarantee acceptable scientific procedures; and provide all the precautions necessary.
>
> The Committee recommends the following guarantees and standards:
>
> a. Study of relevant publications to avoid unnecessary repetitions of experiments;
> b. The physicians conducting experiments should have special knowledge of the problem and be completely responsible;
> c. Good organization and execution;
> d. Every available aid for special or emergency treatment of the experimental subject should be available.

Prior to experimentation the following aspects should be considered:

1. Can the experiment, wholly or partly, be carried out on animals?
2. What is the minimum requirement to obtain the observation? Is its importance and durations ethically justifiable?
3. What is the minimum requirement in altering the conditions of the experiment?
4. Are the requirements for the observation and the alterations of conditions the same?
5. What arrangements are planned? Is the project the fruit of mature thought and expert advice?
6. How will the results be used in obtaining a definite conclusion?

Risk, inconvenience or pain for the subject should be governed by these principles:

a. The investigator's responsibility is more important than the willingness of the subject to accept the conditions;
b. The investigator should consult other experts on the research project in order to intensify the sense of responsibility;
c. The subject must be fully informed and must consent freely;
d. If considerable risk is involved, the experiment is not in accord with the object and purpose of medicine;
e. A practicing physician should not become an investigator on his own patient, if the experiment involves danger. A body of advisers should be consulted;
f. Experiments should be discontinued if the subject so desires or if unexpected danger is encountered, activities the consequences of which cannot be undone, and which therefore cannot be discontinued, and therefore disapproved;
g. Any suffering or danger not strictly inevitable must be prevented;
h. Experiments on children; in institutions for children, old people, etc.; on the insane; or on prisoners, which involve dangerous risks, inconvenience or pain are not approved. All experiments on the dying under any circumstances are disapproved;
i. The "utmost restraint" must be exercised in experiments on patients deemed to have an incurable malady, even though they volunteer as subjects;
j. Unnecessary examinations should be avoided, and diagnostic activities that may be dangerous are justified only if they result in effective therapy. In routine examinations new methods that are dangerous should be strictly limited.

The following additions are suggested: 1. Patients who are soon to die or who are in imminent danger of death should not be considered suitable subjects for research unless it is intended to benefit themselves. Potentially useful procedures might thus be unjustly blamed and the reputation of the investigator be damaged. 2. As a general principle, subjects with an unrelated disease should not be utilized for investigation involving another disease.

The principle codes have been presented above. The armed services in the United States and one or two state organizations abroad have classified codes which cannot be quoted. Such codes as I have seen do not contain anything not presented here.

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J.Am.Med.Assoc. 169:126/478 (Jan. 31) 1959.

Chemical Laboratory

The following paper has been authorized for publication by the Chemical Laboratory.

WALTER WOLMAN, PH.D., *Director.*

IDENTIFICATION GUIDE FOR SOLID DOSAGE FORMS

JOHN J. HEFFERREN, PH.D., CHICAGO

► THE NEED TO IDENTIFY rapidly an unknown tablet or capsule frequently occurs in a wide variety of circumstances. In such cases, a qualitative chemical analysis followed by confirmation tests frequently is a long and difficult task. The time factor, coupled with the limited quantities of the unknown, makes the identification difficult and often impossible.

Methods to aid in identification have involved direct comparisons of the unknown with pictures of known products[1] or with authentic samples carried on various types of display boards. Such methods may suggest the identity of the unknown or eliminate a few possibilities, and in this way they are of some value in identification work but are necessarily limited in scope.

Chemist, American Medical Association.

Development of Identity Guide

As a possible aid in drug dosage identification work occasionally undertaken by the A. M. A. Chemical Laboratory, the feasibility of a preliminary screening method, based solely on the physical characteristics of solid drug dosage forms such as tablets and capsules, was investigated. Examination of a number of commercial tablets and capsules quickly made it evident that there were sufficient differences in the several physical characteristics to suggest reliance on them in an identification or screening procedure. To test these initial observations, 100 products were examined and catalogued according to their physical characteristics.

Since the results were encouraging, the study was then extended to 500 samples. These samples, including both prescription and proprietary drugs, were obtained from the

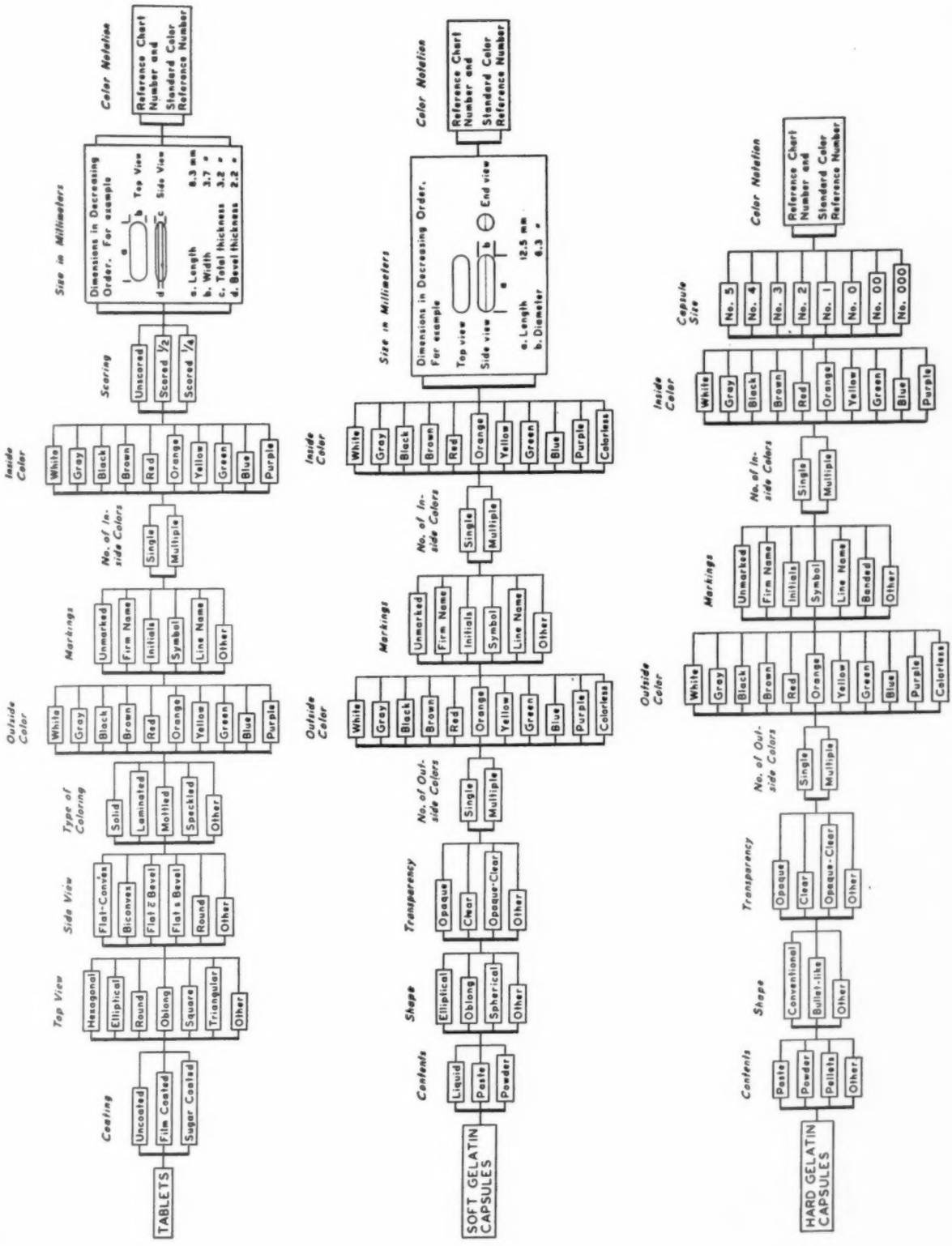

Fig. 1.–Dosage identification guide.

drug files of the Chemical Laboratory, physician's samples, and from a commercial drug store. The samples were not selected according to any use-frequency statistics but on the basis of a representative cross section of the physical characteristics of the tablets and capsules.

From the experience gained in examining these 500 products, a dosage identification guide was developed. This system helps one to identify an unknown by following through a series of categories of physical characteristics, with the consequent elimination of many individual drug preparations and the eventual restriction of remaining possibilities to a relative few.

After completion of this pilot study with the 500 products, the dosage identification guide was discussed in detail with representatives of various agencies and specialty groups concerning the feasibility and need for such a scheme in their particular areas. These included physicians, personnel in emergency receiving rooms, the A. M. A. Committee on Toxicology, toxicologists, pharmacists, and medical examiners and representatives of government agencies, poison control centers, the pharmaceutical industry, and law enforcement agencies.

These conferences indicated that such a suggested guide would prove valuable in a number of areas, provided it were available in suitable form. It is planned to make this information available by publication of a text which would include a short discussion of the dosage identification guide, general information on solid drug dosage forms, a set of color reference chips, and data on the physical characteristics of those products examined.

Solid Dosage Identification System

This dosage identification guide (fig. 1) is constructed to accommodate all the individual tablet and capsule preparations on the market. The guide has three main categories: tablets, soft gelatin capsules, and hard gelatin capsules. In each of these categories is listed a number of terms to describe the individual characteristic under such headings as coating, shape, coloring, contents, markings, scoring, and size.

The shapes of the various tablets and capsules used in the dosage identification guide are illustrated in figure 2. When the tablets are viewed from the side, one of the most characteristic differences between sugar-coated, uncoated, and film-coated tablets is easily seen. Since sugar-coated (pan-coated) tablets are coated by tumbling, all the ridges resulting from compression of the core are rounded by subsequent layers of coating material. Film-coated tablets are coated by dipping; thus, they have a thin film coat but retain ridges characteristic of the uncoated tablet. Some forms of sugar-coated tablets are quite similar to soft gelatin capsules. The essential differences are that the soft gelatin capsule has a seam at the point of closure of the two halves, and the contents can be liquid, paste, or powder. The sugar-coated tablet will not have a seam and will have a compressed core.

In the dosage identification guide (fig. 1), the outside and inside color categories have 10 terms for tablets and 11 for capsules. The use of a limited number of colors at this point in the guide is to facilitate indexing. At the far right of the guide is provision for a more exact color notation of the product.

A more exact color notation is obtained by comparison of the colors of the product with a set of reference color chips, which will be included with the identification text. For example, a sugar-coated tablet might be described by using the limited color terms as outside color, red, and inside color, brown, whereas in the color notation category, these two colors might be more accurately described in relation to the reference chips as red no. 2 and tan no. 1 respectively.

The color of each product will also be notated by reference to a commercially available color text. This information will be of value only to those who have that

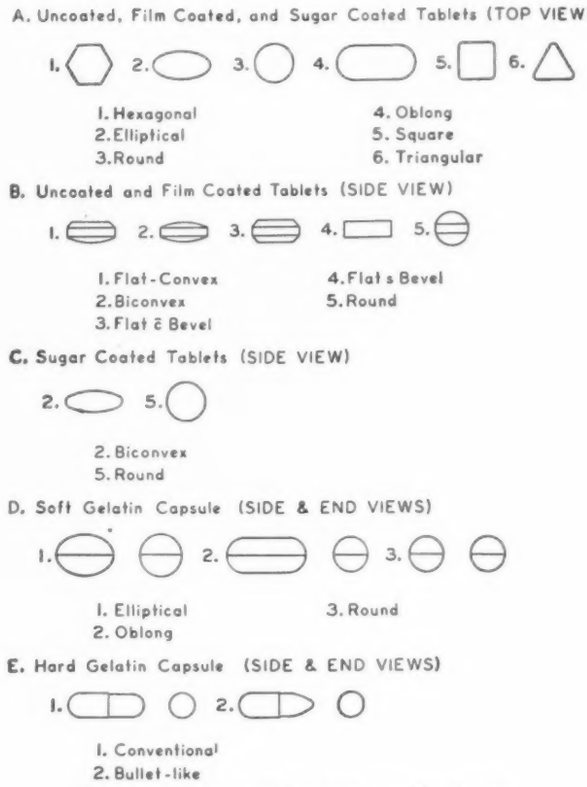

Fig. 2.—Common tablet and capsule shapes.

text and would constitute an auxiliary refinement of the identification guide. This additional color notation system would not be necessary for the normal use of the system.

The data reported for the dimensions of tablets and capsules are subject to three sources of variation. They are variation due to (1) manufacture, (2) limitations of the measuring device, and (3) precision of the measurements. The magnitude of these sources of variability will be dependent, in part, on the particular type of tablet or capsule.

Due to its method of manufacture, the size of an uncoated (pressed powder) tablet is most readily reproduced within the same lot and between lots. The diameter of such a tablet is determined by the diameter of the die used in the compression of the tablet and is usually duplicated to within 0.1 mm. On the other hand, the total thickness is a less accurate dimension because of manufacturing variables such as granulation density. The duplication of this dimension, however, is usually within 0.3 mm., depending to some extent on the size of the tablet. The measurement at the bevel edge is related to and has the same variables as that of the total thickness, plus the added variable due to greater difficulty in obtaining as accurate a reading at the edge with a measuring device. With uncoated, pressed powder tablets, the dimensions in decreasing order of reproducibility are diameter, total thickness, and bevel thickness.

With film-coated and sugar-coated tablets and soft gelatin capsules, a wider range of dimensional variability results because of the methods of manufacture. These products

(with the exception of film-coated tablets) do not have a bevel measurement and as a result have one less dimension than does the comparable shape in an uncoated tablet. Thus, the dimensions of film-coated and sugar-coated tablets and soft gelatin capsules are somewhat less definitive than

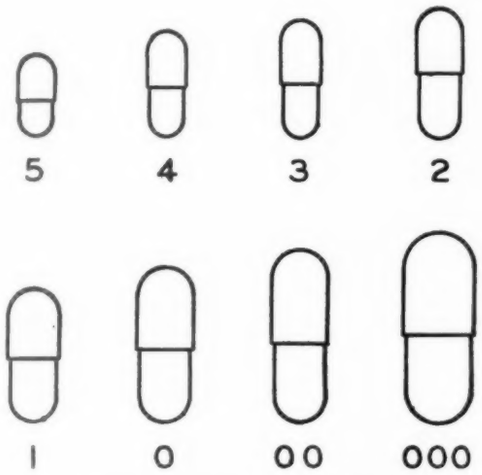

Fig. 3.—Standard capsule sizes (actual size).

are those of an uncoated tablet; however, this is somewhat offset by the many colors and types of contents which these products usually have.

All measurements of tablets and soft gelatin capsules are made with a vernier calipers reading to 0.1 mm. The size of a hard gelatin capsule is determined by comparison to a chart of standard capsule sizes (fig. 3). These capsule sizes are accepted throughout the pharmaceutical industry and represent the most convenient way to describe the size of a hard gelatin capsule.

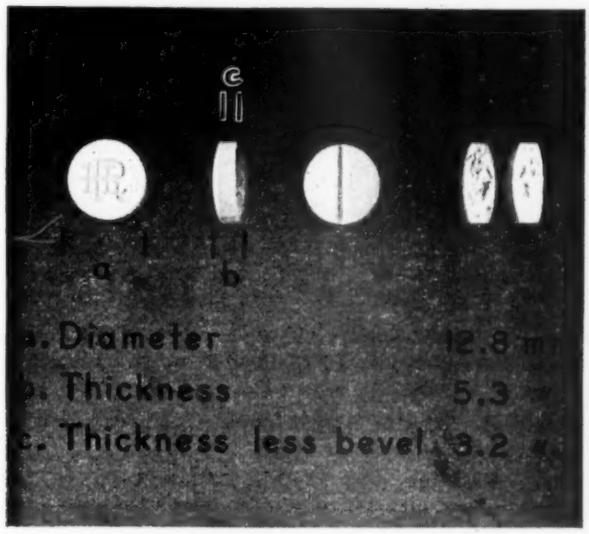

Fig. 4.—Physical characteristics of sample tablet.

Application of Dosage Identification Guide

To illustrate the application of the dosage identification guide to a specific problem of identification, the commercially available tablet pictured in figure 4 can be used as an example of an unknown. Using the guide, figure 1, the term best describing this tablet in each category such as coating, top view, etc., is selected. For this tablet, the

— TABLETS —

Uncoated, Round, Biconvex, White, Scored - ½, Marked

MARKINGS	SIZE IN mm	TRADE NAME	DOSAGE	FIRM
A	7.2 3.0 1.4	Theruhistin	4 mg.	Ayerst
A	6.4 2.6 1.0	Arlidin	6 mg.	Arlington Funk
HR	12.8 5.3 3.2	Gantrisin	0.5 gm.	Hoffmann LaRoche
W	8.0 4.0 2.3	Hedulin	50 mg.	Walker
U	6.4 2.7 1.8	Delta-Cortef	5 mg.	Upjohn
RIKER	11.2 5.3 3.2	Calcium Disodium Versenate	0.5 gm.	Riker
TABLOID BRAND	7.5 3.1 2.0	Daraprim	25 mg.	Burroughs Wellcome

Fig. 5.—Idealized page of future text on identification of solid dosage forms.

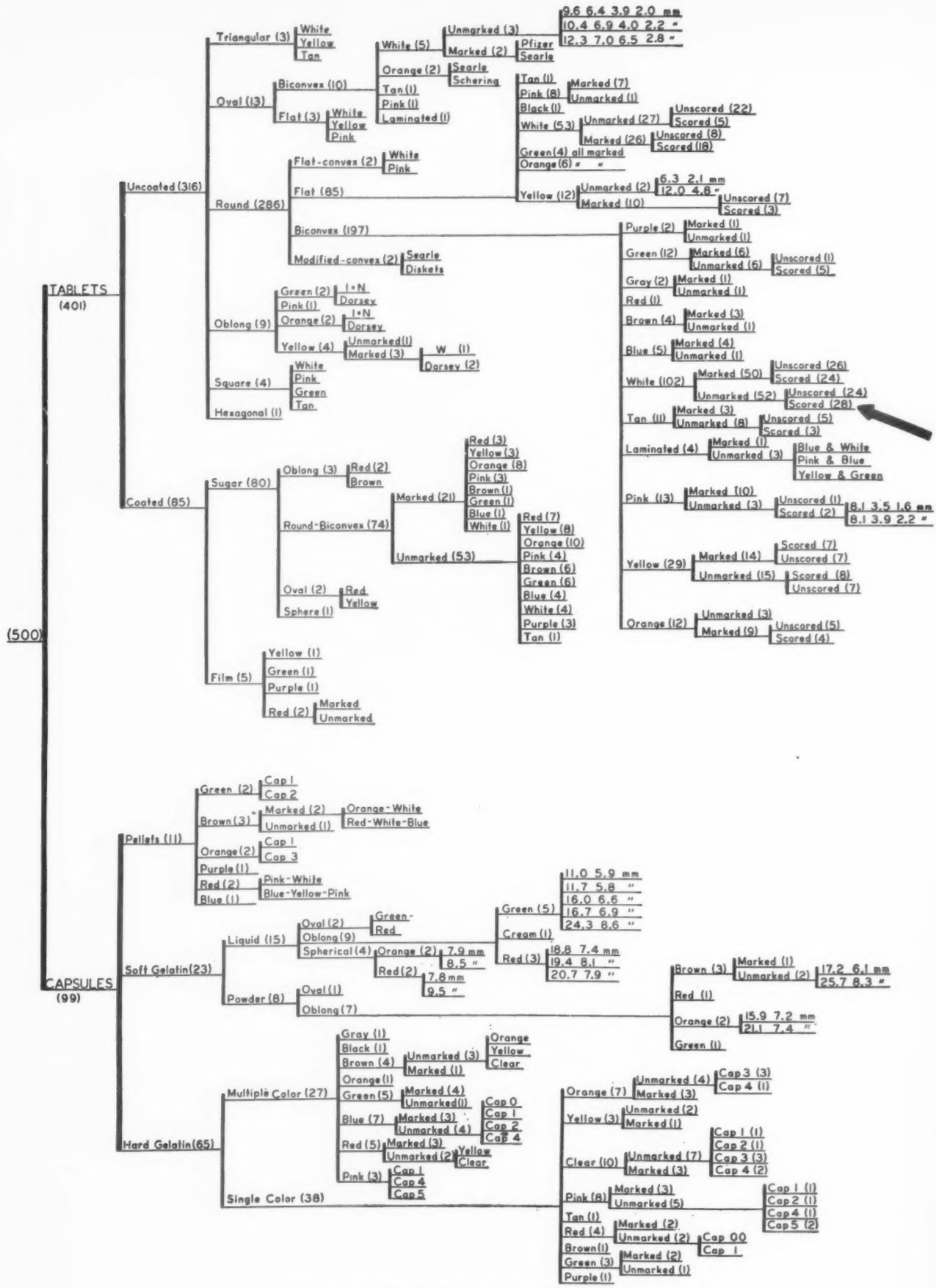

Fig. 6.—Breakdown of 500 products used in pilot study.

terms and the corresponding categories of physical classification would be as follows:

Coating	uncoated	No. of inside colors	single
Top view	round	Inside color	white
Side view	biconvex	Scoring	scored-½
Type of coating	solid	Dimensions	12.8, 5.3, 3.2mm.
Outside color	white	Color notation	white
Markings	initials		

After the selection of those terms best describing the physical characteristics of this tablet, the text containing similarly obtained listings for commercially available tablets and capsules is referred to for the possible solution to the identity of the unknown. An abbreviated and idealized page of this text might look like that shown in figure 5. This page contains a listing of tablets which are uncoated, round, biconvex, white, marked, and scored-½. The third product listed has the same physical characteristics, markings, and dimensions as the tablet in figure 4, so the tablet is probably the 0.5-Gm. tablet of sulfisoxazole (Gantrisin) manufactured by Hoffmann-LaRoche. Positive identification of this tablet should then be made by some confirmatory test.

In figure 6, the application of this guide and text to 500 products demonstrated its workability with a variety of tablets and capsules, ranging from the unusually shaped, well-marked products to the familiarly shaped, unmarked products. Proceeding from left to right across the chart, gradual elimination or separation of the 500 products into groups occurs. The numbers in parentheses on the chart represent the number of individual products remaining in that group.

At the far right of the chart, wherever the break-down ends as marked products, there are still two further aids to identification, that is, the dimensions and the actual markings such as symbols, initials, or names. In these cases complete separation usually occurs, leaving no two products in the group alike in every physical characteristic utilized by the coding system.

On the other hand, the unmarked categories, such as that indicated by the arrow in figure 6, can be further separated only on the basis of size. This tablet group—uncoated, round, biconvex, white, unmarked, and scored-½—contains 28 products, which is the largest group in the sampling of 500 products.

The sizes of these 28 products are listed in figure 7. The first 4 of these products have the same diameter of 8.0 mm., whereas the other 24 products are sufficiently different to be eliminated by this first measurement. The thickness of the first and fourth separate them from the second and third products; however, the third measurement fails to achieve any further separation. Reference to the text will indicate what the drug compositions may be. Identification is then relatively simple by application of confirmatory tests for these substances.

There are eight tablets in figure 7 with a diameter between 10.4 mm. and 10.6 mm. Thickness measurements eliminate three of these products (4.0, 4.8, 4.9); thus, the remaining five represent 1% of the 500 products used in this initial study. It is recognized that when thousands of samples instead of 500 are examined and coded into the scheme, the total number of individual products in such a nondistinguishable group will be much greater, even though the percentage of the total may not change.

Present Status

The examination and coding of commercial drug products is under way. A list and samples of those drugs which represent approximately 87% of the prescription drugs used have been obtained and coded. The same approach is being applied to the proprietary drugs. With these most frequently used drugs as a core, coding is extending to other commercially available tablets and capsules.

Extension of the coding system to include other solid drug dosage forms such as suppositories is planned. Some nondrug products such as plant foods, which are now commercially available in tablets and capsules, will also be included.

It is planned that all the data obtained from coding the physical characteristics of these products will be organized and published in text form together with the dosage identification guide, color reference chips, and instructions for use. It is hoped that the first edition of this text including some 5,000 listings will be published in about a year. Thereafter, supplements and new editions will be published to include new products and those old products whose physical characteristics will have been changed. Further editions will be expanded then to include all the commercial drug products obtainable.

1	2	3	1	2	3
8.0	3.0	1.2	10.5	4.5	2.6
8.0	3.5	2.0	10.5	4.9	2.4
8.0	3.7	2.0	10.6	4.8	2.8
8.0	4.3	2.1	11.1	4.6	2.5
8.8	3.6	1.9	11.1	5.9	3.9
8.8	3.6	2.0	11.2	4.9	3.2
8.8	3.7	2.0	11.2	5.0	3.1
8.9	3.4	1.5	11.2	5.4	3.4
9.6	4.3	2.3	11.2	5.9	4.2
10.4	4.3	2.3	12.8	5.0	3.0
10.4	4.4	2.5	12.8	5.1	3.0
10.4	4.5	2.6	12.8	5.6	2.6
10.5	4.0	2.0	16.0	6.7	4.0
10.5	4.4	2.4	17.7	8.7	3.4

1-Diameter in mm, 2-Thickness in mm, 3-Bevel Thickness in mm

Fig. 7.—Dimensions of uncoated, round, biconvex, white, unmarked, and scored-½ tablets.

The success of this project depends on obtaining authentic drug samples. This is one of the most difficult problems in this work, and it is hoped that samples will be made available to us by the many firms, individuals, and agencies who have such products. At least six individual tablets and capsules of each size, the name of the product and of the manufacturer, and dosage size are essential for coding purposes.

The color reference chips used in the text will be selected and prepared with the assistance and advice of Mr. Carl Foss, Princeton, N. J.

The list representing 87% of prescription drugs used in this study was developed and contributed by Mr. David D. Stiles of Abbott Laboratories, North Chicago, Ill., from a prescription survey project carried out under his direction.

The samples of these prescription drugs were gathered and contributed by Sargent's Drug Stores, Inc., Chicago, through the courtesy of Mr. William Morse.

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J. Am. Med. Assoc. 169:127/479 (Jan. 31) 1959.

POSITIONS

in hospital pharmacy

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The Personnel Placement Service is operated without charge for the benefit of hospitals and pharmacist members of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. The ultimate purpose is the improvement of pharmaceutical services in hospitals, by more adequately fulfilling hospital pharmacy personnel needs and by locating positions which provide challenging opportunities for pharmacists who have indicated an interest in a hospital career.

By participating in the service, the hospital indicates a desire to achieve a pharmaceutical service which meets the Minimum Standard for Pharmacies in Hospitals. A description of the position should be submitted to the Division of Hospital Pharmacy on the forms provided. The hospital will receive applications directly from the applicant. The hospital agrees to reply to each application received and to notify the Division of Hospital Pharmacy when the position is filled.

The pharmacist, by participating, agrees to submit a Personnel Placement Service Information Form to the Division of Hospital Pharmacy. The applicant will then be notified of openings listed with the Service as they become available and can negotiate directly with the hospital if he is interested. It is agreed that the Division of Hospital Pharmacy will be notified as soon as a position is accepted.

A listing of positions open and wanted will be made regularly in the AMERICAN JOURNAL OF HOSPITAL PHARMACY without charge. Neither the name of the hospital offering the position nor the name of the applicant will be listed, except by code. All inquiries should be directed as shown below, including the code number.

Address all inquiries to
Division of Hospital Pharmacy
2215 Constitution Avenue, N. W.
Washington 7, D.C.

positions open

CHIEF PHARMACIST—350 bed hospital. Must be eligible for licensure in N.J.; interest in manufacturing; 44-hour week, 2 weeks' vacation. Salary $5200-$5700. PO-6

STAFF PHARMACIST—550 bed general hospital located in Ohio. 40-hour week; 2 weeks' vacation. Salary $400-$450. PO-34

ASST. CHIEF PHARMACIST—310 bed general hospital located in Va. 40-hour week, 2 weeks' vacation, 3 weeks' sick leave, 6 holidays. Salary $5,000 to $6,000. Also
STAFF PHARMACIST—259 bed hospital located in Va. Hospital experience preferred. 40-hour week, 2 weeks' vacation. Salary open. PO-35

STAFF PHARMACIST—460 bed general hospital in Mass. 40 hour week 2 weeks' vacation; other benefits. PO-40

ASST. CHIEF PHARMACIST—Large voluntary hospital located in Brooklyn; N.Y. registration required. Supervisory ability needed. 35-hour week, 2 weeks' vacation, 10 days' sick leave, 9 holidays. PO-51

CHIEF PHARMACIST—88 bed hospital located in Pa. Planning expansion to 125 beds for general patients and 40 beds for chronic patients. Possibility for pharmacist to serve as Asst. Administrator in charge of Purchasing, Central Supply and Store Room. 40 hour week; 2-4 weeks' vacation. Young man preferred. Salary open. PO-59

STAFF PHARMACIST—325 bed research hospital. Min. 2 years' experience preferably in hospital pharmacy. N.Y. registration required. Manufacturing sterile solutions and assisting in product development. Salary $4770-$5860 plus benefits. Research work beyond 40-hour week available at $3.00 per hour. PO-61

ASST. CHIEF PHARMACIST—100 bed general hospital. Ind. registration required. Young lady preferred. Hospital experience not necessary. Main area of responsibility in Central Supply and Solution Manufacturing. 40 hour week, 3 weeks' vacation. PO-63

PHARMACIST—Animal hospital located in Colo. Duties include maintaining drug stock and checkout service, also willing to help students. 44 hour week, 4 weeks' vacation. Salary $5,000. PO-64

CHIEF PHARMACIST—325 bed general hospital. Eligible for registration N.Y. Hospital experience desirable but not necessary. 40-hour week, 2 weeks' vacation. Salary dependent upon qualifications. PO-70

ASST. CHIEF PHARMACIST—313 bed general hospital. Eligible Ky. registration. Previous hospital experience not necessary. 40-hour week, 2 weeks' vacation. Salary $400-$500, benefits. PO-73

CHIEF PHARMACIST—265 bed general hospital. Varied duties including teaching if interested. No experience required. 40-hour week, 2 weeks' vacation. Salary $400 (approx.) plus benefits. PO-74

STAFF PHARMACIST—335 bed hospital located in Fla. Duties include responsibilities in outpatient department and parenteral solution room. 40-44 hour week, 2 weeks' vacation; 1 meal daily. Salary $5200. PO-75

ASST. CHIEF PHARMACIST—237 bed general hospital in West Va. Female desired. 44-hour week; 2 weeks' vacation. PO-77

STAFF PHARMACIST—503 bed general hospital. Inpatient and outpatient prescriptions; manufacture of some injectibles. Male or female. Interested in recent graduate with hospital experience desirable but not required. 40-hour week; 2 weeks' vacation; other benefits. PO-78

CHIEF PHARMACIST—320 bed general hospital located in Iowa. Experience or internship in hospital pharmacy required. 40-44 hour week, 2 weeks' vacation, other benefits. Salary open. PO-80

STAFF PHARMACIST—316 bed general hospital. Eligible registration in Minnesota. Some manufacturing; 40-hour week 2 weeks' vacation; other benefits. Salary open. PO-81

STAFF PHARMACIST—295 bed hospital expanding to 500 in future. Eligible for registration in Mich. Experience in hospital pharmacy and manufacturing preferred. 40-hour week, 2 weeks' vacation. Salary $5720. PO-86

CHIEF PHARMACIST—400 bed general hospital. B.S. required. Internship in hospital pharmacy preferred. Eligible for Tex. registration. 40-hour week, 2 weeks' vacation. Salary up to $6,500 to start. PO-90

ASST. CHIEF PHARMACIST—315 bed general hospital. Registration in Iowa required. Experience desirable but not essential. 40-hour week, 2 weeks' vacation. Salary $450. PO-92

ASST. CHIEF PHARMACIST—185 bed general hospital. Must be eligible for licensure in Ind. B.S. required. 40-hour week. Salary $4500-$5500. PO-94

STAFF PHARMACIST—500 bed general hospital located in Okla. B.S. required. 40-hour week, salary open. PO-95

STAFF PHARMACIST—400 bed general hospital. Eligible registration in Fla. 40-hour week, salary open. PO-96

CHIEF PHARMACIST—425 bed hospital. Male preferred. Mo. registration. Will train good applicant without experience. 40-hour week. Salary open. PO-98

STAFF PHARMACIST—400 bed general hospital located in Iowa. 40-hour week, 2 weeks' vacation. Salary open. PO-99

CHIEF PHARMACIST—200 bed general hospital. Male or female considered. Prefer hospital experience. Salary $5500. 44-hour week, vacation, sick leave. PO-100

ASST. CHIEF PHARMACIST—152 bed general hospital expanding to 180 beds. Registration in Neb. required. 40-hour week, 2 weeks' vacation. Salary open. PO-101

CHIEF PHARMACIST—73 bed general hospital. Complete responsibility of Pharmacy Dept. 44-hour week, 2 weeks' vacation. Salary open. PO-102

STAFF PHARMACIST—215 bed general hospital expanding to 35 more beds. N. Y. registration required as well as hospital experience. 40 hour week, 2 weeks' vacation. Salary open. PO-104

STAFF PHARMACIST—425 bed general hospital located in Tex. 40-hour week, 2 weeks' vacation. Salary $425-$500. PO-105

CHIEF PHARMACIST—244 bed hospital. California registration required. Complete charge of pharmacy including all purchasing. 40-hour week, 2 weeks' vacation. Salary $505-$613. PO-106

STAFF PHARMACIST—585 bed general hospital located in Ore. One year hospital pharmacy experience required. Salary open. PO-107

STAFF PHARMACIST—320 bed general hospital. Must be eligible for State of Wash. license. Experience in hospital pharmacy desirable. 40-hour week, 2 weeks' vacation, other benefits. Salary $6300-$7380. PO-110

STAFF PHARMACISTS—Two—Eligible for licensure in West Va. and Ky. Salaries good. PO-111

CHIEF PHARMACIST—340 bed general hospital in south; affiliated with medical school; outpatient clinic; hospital pharmacy internship program. Salary $6,600-$7,000. PO-112

STAFF PHARMACST—300 bed, short term general hospital. Pharmacy encompasses Central Supply Oxygen and Inhalation Therapy and Orthopedic equipment, etc. Plans to expand two additional floors with 150 more beds underway. Applicant must be eligible for registration in N.C. Benefits include 2 weeks' vacation, sick leave, group life term insurance, retirement program. 44-hour week. Salary $5100-$5950. PO-113

CHIEF PHARMACIST—150 bed general hospital; to assume complete responsibility for the pharmacy department. Salary $525 per month; 3 weeks' vacation; discount on meals and hospitalization. PO-114

ASST. CHIEF PHARMACIST—425 bed general hospital; duties include dispensing and supervision of special projects. Prefer male applicant with internship in hospital pharmacy. Unique opportunity to obtain experience. Salary $7,000 to $7,500 to start. PO-115

positions wanted

INDIAN PHARMACIST—Desires appointment to obtain higher training in hospital pharmacy; graduate Madras Univ.; 1½ years' experience in 1,000 bed hospital, including inpatient and outpatient dispensing, parenteral and general manufacturing and administration. PW-68

HAITIAN STAFF PHARMACIST—Male, married. Has 5 years' hospital experience. Present owner of pharmacy. Desires to locate in northwest U.S. PW-74

STAFF PHARMACIST—4 years' hospital pharmacy experience; prefers Wash. state (registered). Female married, B.S. pharmacy. PW-87

IRANIAN PHARMACIST—Desires opportunity to continue hospital pharmacy studies; single, age 30; excellent academic background; now studying industrial chemistry Columbia Univ. Prefers location in West or Northeast. PW-88

ASST. PHARMACIST—Female, married. Educated and trained in Philippines. Served hospital pharmacy internship. Registered Manila. Desires to locate East Coast of U.S. PW-91

CHIEF PHARMACIST—Prefers small hospital in Ohio. Male, married. B.S.; registered Ohio. Excellent academic and professional background. PW-93

STAFF PHARMACIST OR ASST. CHIEF—Female, single, Filipino, educated and trained Philippines. 10 years' hospital experience. Served hospital pharmacy internship. PW-95

PHARMACIST—Male, married. Registered Ill. Desires to locate in New England. PW-102

STAFF PHARMACIST—Single female, registered Mo. B.S.; hospital pharmacy experienced. Desires locate Midwest. PW-104

CHIEF PHARMACIST—Female, single registered Penna. 12 years' experience Chief Pharm. Desires to locate in Penna. or Ohio. PW-111

CHIEF OR ASST. CHIEF PHARMACIST—Male, married, registered Mich. and Ariz. Served hospital pharmacy internship. Retail experience plus 7 years' hospital pharmacy experience. PW-113

STAFF PHARMACIST—Male, married, registered Mass. Retail and hospital pharmacy experience. Desires locate East or Northeast. PW-114

CHIEF OR STAFF PHARMACIST—Female, single, registered Tex. Desires to locate in East. PW-115

STAFF PHARMACIST—Female, single, B.S. Retail experience only. Registered Fla. PW-116

ASST. CHIEF PHARMACIST—Male, single. B.S. Vet. Adm. Hosp. experience. Registered Va. and Washington, D.C. PW-117

STAFF PHARMACIST—Male, married. B.S. registered La., Va., and Washington, D.C. PW-118

ASST. DIRECTOR OR DIRECTOR OF PHARMACY SERVICES—Male, single, B.S. Retail and 4 years' hospital experience. Registered, Ill. PW-119

ADMINISTRATOR—Male, married, D.Sc. 15 years' hospital pharmacist. Desires locate Fla. PW-120

PHARMACIST—Male, single. B.S. Registered Maine. Served hospital pharmacy internship. PW-122

CHIEF PHARMACIST—Male, single. Registered Conn. and N. J. 10 years' hospital pharmacy experience, B.S. PW-123

CHIEF PHARMACIST—Male, single. 10 years' hospital pharmacy experience. 1 year pharmacy internship. Registered Ariz., Ga., New Mexico, prefers south. PW-124

CHIEF PHARMACIST—Female, single. B.S. 2 years' hospital experience. Registered Ohio. Prefers Ohio or Ill. PW-126

PHARMACIST—Female, Filipino, recent graduate Manila Central Univ. Would like to locate in western part of U. S. PW-127

PHARMACIST—Male, married. Registered Mass., D.C. and Md. Will locate any part of U. S. Served hospital pharmacy internship. Over 20 years hospital pharmacy experience. PW-128

STAFF PHARMACIST—Male, married. Several years hospital pharmacy experience. Registered Mich. PW-129

ASST. CHIEF PHARMACIST—Male, single, registered Neb. and Pa. Background of hospital and retail pharmacy. Has M.S. pharmacy. Desires Midwest location. PW-133

STAFF PHARMACIST—Female, married, registered Kansas. 4 years hospital pharmacy experience. PW-136

CHIEF PHARMACIST—Male, married, registered Ark. B.S. pharmacy. 5 years experience as Chief Pharmacist. PW-137

ASST. CHIEF PHARMACIST IN LARGE HOSPITAL OR CHIEF PHARMACIST IN SMALLER HOSPITAL—Available in June. B.S. Chemistry, B.S. Pharmacy, M.S. Hospital Pharmacy. Completing internship at Johns Hopkins Hospital. Single; completed military obligation. Will locate anywhere. PW-138

CHIEF PHARMACIST—Male, married. Registered Wis. Ph.D. Several years' hospital pharmacy experience. Locate any section of the country. PW-139

CHIEF PHARMACIST—Male, married. B.S. Conn. registration. 5 years' hospital pharmacy experience. Prefers Northeast section of country. PW-140

STAFF PHARMACIST—Male, single. Registered N.Y. and Me. B.S. Served Hospital Pharmacy Internship. PW-141

ASST. CHIEF PHARMACIST—Male, married. B.S. Pharmacy. Registered N.Y. Hospital and retail experience. Locate N.Y. state. PW-142

STAFF PHARMACIST—Female, single. Registered Philippines. M. S. Pharmacy, St. Louis Coll. of Pharm. Locate any section of country. PW-143

CHIEF PHARMACIST—Prefers N.Y or N.J. area. Over 20 years' experience as chief pharmacist and purchasing agent. Graduate St. John's Univ., Coll. of Pharm. and registered in N.Y. and N.J. PW-144

CHIEF PHARMACIST—Registered in N.J.; any location; 6 years' experience in hospital pharmacy. PW-145

STAFF PHARMACIST—Male, single. Completed military requirements. Hospital pharmacy experience. Prefers east. PW-146

CHIEF PHARMACIST—Registered in Mo. and Ill. Ph. G. degree; 8 years' experience in hospital pharmacy. PW-147

ASST. CHIEF OR CHIEF PHARMACIST—Single male. Registered in D.C., Ill., Md., and Pa. Graduate Univ. of Pittsburgh in 1953; experience in research; prefers north and east. PW-148

PHARMACIST—Male, single B.S. pharmacy June, 1959. Locate east. PW-149

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